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Editorial

Emotional Stress and the Etiology of Coronary Artery Disease

TWO major theories of causation of coronary atherosclerosis are now popular. One relates the pathology to an abnormal lipid level in the blood, either total lipid or some fraction of lipoprotein. The other, that of the school of Rokitansky[1] and Duguid,[2] considers the cholesterol deposit to be secondary to the damage from repeated thrombotic injury ineffectively neutralized by normal fibrinolytic mechanisms. It is possible that both of these may be related in some way to abnormalities of fat metabolism in that thrombotic episodes appear to be more common in populations with high fat intakes.

There seems to be some pressure, by those psychosomatically oriented, to admit the camel of atherosclerosis into the spiritual tent, even though, up to now, his nose is the only part even suggestively inside. By this I mean that emotional stress is being proposed as the agent through which lipids appear in coronary vessels, and that is why coronary disease is increasing in what is supposed to be an unusually anxious age in world history. Just how this happens we are yet to be told.

This point of view presents dangers. It is an easy way out because it almost precludes scientific investigation. No one can prove that our age is more troubled than many before it. No one can measure emotional stress, since it has no meaning except in relation to him who is stressed. Furthermore, it creates the belief that emotional stress is a bad thing. Therefore, not only are pain, anxiety, gr[illegible] fear, anger, and frustration undesirable, bu[illegible]o also must be joy, pride, success, striving, and love.

I confine this discussion to the question of the fundamental etiology of coronary disease, not wishing to enter the murky area concerned with the events purported to initiate an isolated acute myocardial infarction.

What are some of the facts? Cannon and Mendenhall[3] from their work of over 40 years ago, are the authorities quoted to indicate that normal reactions to emotional stimuli are protective but may be deleterious. For example, blood coagulability is increased by pain and therefore this leads to coronary thrombosis. Yet, from a practical standpoint, not one of the many tests of blood coagulation has been able to show that a patient suffering from either an overt myocardial infarct, or prolonged anginal pain, has increased clotting of his blood.*

Perhaps I am reversing myself, since I said that no one can measure emotional stress, yet there are situations that almost everyone would consider indicative of spiritual disturbance. One of these is suicide. It is reported that in Japan hypertension is prevalent, and so is suicide, but coronary disease is rare.[4] Manic depressive psychosis shows, in both its agitated and depressed phases, severe

*McDonald and Edgill (Lancet 278: 457, 1957) report "increased coagulability of the blood has been demonstrated between a group of patients with ischaemic heart disease and healthy controls." However, this was true in respect to statistical comparison only of both groups and in only some of the total battery of tests employed. No patients with recent cardiac infarction were included. There was considerable overlapping of results in the two groups and in some patients with ischemic heart disease the coagulability was actually less than in the controls by some tests.

turmoil, and yet these patients, if properly fed and nursed, do not succumb to coronary disease to any greater extent than does the general population; indeed their life expectancy is the same.[5] Neurocirculatory asthenia, which many agree is an anxiety neurosis, does not lead to coronary disease nor to "hypertension, peptic ulcer, asthma, ulcerative colitis or thyrotoxicosis, which some authors have speculated are caused by 'anxiety.'"[6] Prisoners in Federal penitentiaries had the lowest incidence of new coronary disease of all groups in the lipoprotein study.[7] The incidence of fatal coronary attacks was reduced in the occupied Scandinavian countries in wartime—certainly a stressful period. Primitive races with oppressive tabus, terrifying witchcraft, and "uncivilized" customs are not prone to coronary disease.

Anxiety appears either to have no influence on blood coagulation or it may favor fibrinolysis[8–10]—a protective enzymatic response. It is reported that in patients with recurrent thrombophlebitis, stressful situations produced attacks. In hypertensive patients in whom stressful interviews caused a rise in blood pressure there was slight increase in blood coagulability and viscosity but not in other hypertensive patients nor in people suffering from other "stress" diseases.[11]

It seems likely that emotional tension results in compulsive eating, drinking, and smoking in many individuals as compensation for anxiety, and I believe that it is through this indirect mechanism that stress has its influence on coronary disease. In addition it contributes to the failure to achieve daily physical exercise by promoting fatigue and by forcing a man to make so many commitments that no time is found for exercise, such as walking.

The danger of attributing cardiovascular disease to emotional tension is that it makes everyone fearful lest he find himself in a situation of anxiety, and it fosters a belief that struggle and achievement are lethal, whereas they are probably healthy. It plays into the hands of those who would have us believe that work causes heart disease. Authoritative opinion denies this.[12]

Stress is not new. What is new is coronary thrombosis. Over one hundred years ago Thoreau wrote "The mass of men lead lives of quiet desperation" but these men were apparently not dying of coronary disease in great numbers in 1854.

Recently a report[13] from the Air Force indicated that certain officers under stress had elevated serum cholesterol levels, but it should be noted that 75 per cent of these returned to a normal range when the subjects were placed on a regimen of more rigid diet and exercise. Similarly, a claim has been made that stress raised serum cholesterol in a group of patients who reacted by a lowering of the lipid under a proper "physician-patient relationship."[14]

Dutch investigators have contributed to this by combining observations on diet and "stress."[15] They state, "A 'reaction pattern' was described which seemed to occur both in infections and in physical and emotional forms of 'stress.' During or immediately after the infection, exertion or emotional tension, the serum cholesterol tended to fall; when the 'stress' period was at an end, i.e. during convalescence, usually after three or four weeks, there occurred a rise of the blood cholesterol, which often exceeded the original value and persisted for two or more weeks."

After discussing the possible significance of elevated serum cholesterol in the genesis of atherosclerosis they say, "Finally by demonstrating the influence of both nutrition and stress on the serum cholesterol our observations might bridge the gap between those authors who have regarded atherosclerosis as of nutritional origin only and those who have pointed out its frequent occurrence among patients who have labored under strain."

In any event, it seems to me that the normal reactivity of serum cholesterol under many influences makes it extremely difficult to draw conclusions about any one individual. Population studies showing a correlation between coronary and thrombotic disease, serum cholesterol level and diet are impressive. No other

variable in the complex atherosclerotic equation seems to me as yet so suggestive.

The defense mechanisms in Cannon's emotional cats were explained as mediated through epinephrine discharge producing shortening of clotting time, but it must be remembered that epinephrine, or severe physical effort as its activator, is also a potent inducer of fibrinolysis. Duguid, indeed, believes that acute coronary thrombosis is not due to a general hypercoagulable state, since he finds fluid blood in the coronary vessel distal to the occluding thrombus.

Psychiatric analysis of our group of young coronary victims resulted in this conclusion: "No one yet has demonstrated in humans that stresses of a magnitude compatible with a 'normal' life can influence the deposition of cholesterol material in coronary vessel walls."[16] The authors noted possible effects of increased heart rate and output, rise in blood pressure, shortened clotting time, and increased blood viscosity but stated "We simply do not have evidence, however, that anxiety or other emotional stress is related to the genesis of the atherosclerosis."

Even in a field perhaps more contentious than that of the etiology of coronary atherosclerosis, namely, hypertension, we find a very wise psychiatrist saying, "The fact that acute emotional excitement may result in transitory elevations of blood pressure should not be used as a basis for the inference that long standing emotional states or conflictive situations can act as precipitants to chronic vasomotor constriction."[17]

I believe we should leave it there at present. Undoubtedly much of the wishful thinking about work and stress being evil is an *Old Testament* guilt that labor is part of the penalty for original sin, which is not successfully nullified by the Puritan concept of the nobility of struggle and ambition. We hope that work and anxiety are bad for us so that we can avoid them, or blame them for ills brought upon us by our own vices. But Adam and Eve were expelled from the Garden of Eden not because they had eaten the fruit of the Tree of Knowledge, and therefore had to work for a living, but because of the Lord's fear that they might also eat the fruit of the Tree of Life and live forever in spite of stress.

Corvisart,[18] 150 years ago, attributed all heart disease to two principal causes, "from the action of the organ and from the passions of man." He believed that the heart could be injured (among other things) by crying in infancy, wrestling, fencing, playing wind instruments, laughing, weeping, reading, declamation, and "every kind of effort;" as well as by "anger, madness, fear, jealousy, terror, love, despair, joy, avarice, cupidity, ambition [and] revenge." But he quite honestly avers that "to conceive man without passions, is to conceive a being without his attributes."

The complexity of man makes etiologic dogmatism untenable in any disease and we all admit the influence of an acute emotional stimulus upon endocrine mechanisms, but I consider that the following is currently correct: "No technics have been developed as yet for use in this field which permit conclusive observations concerning the exact relationship, if any, of life situations, and emotion-provoking situations to this disorder [neurocirculatory asthenia] or which allow for a definite statement as to whether an illness is or is not on a 'psychogenic' basis."[6]

It would be a good thing if more people really knew what Selye means by "stress" and if they would read the inscription in the front of his book *The Stress of Life*, which he says is "dedicated to those who are not afraid to enjoy the stress of a full life, nor too naive to think that they can do so without intellectual effort."[19]

HOWARD B. SPRAGUE

REFERENCES

1. ROKITANSKY, C.: Lehrbuch der pathologische Anatomie. Vienna, 1841-1846.
2. DUGUID, J. B.: Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J. Path. Bact. **58**: 207, 1946.
3. CANNON, W. B. AND MENDENHALL, W. L.: Factors affecting the coagulation time of the blood. Am. J. Physiol. **34**: 251, 1914.

4. KEYS, A.: Cardiovascular Epidemiology. New York, Paul B. Hoeber, Inc., 1956, p. 182.
5. GILDEA, E. F.: Personal communication.
6. COHEN, M. E. AND WHITE, P. D.: Life situations, emotions, and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). Psychosom. Med. **13**: 355, 1951.
7. Report of the cooperative study of lipoproteins and atherosclerosis. Circulation **14**: 691, 1956.
8. TRUELOVE, S. C.: The lability of human fibrinolysin. Clin. Sc. **12**: 75, 1953.
9. MACFARLANE, R. G. AND BIGGS, R.: Fibrinolysis—its mechanism and significance. Blood **3**: 1167, 1948.
10. ASTRUP, T.: The biological significance of fibrinolysis. Lancet **2**: 565, 1956.
11. SCHNEIDER, R. A.: Recurrent thrombophlebitis: An experimental study of life situations and emotions and the clotting time and relative viscosity of the blood. Am. J. Med. Sc. **222**: 562, 1951.
12. Costs, Operations, and Procedures under The Workmen's Compensation Law of the State of New York. Moreland Report. January 28, 1957, p. 104 Appendix A—The Cardiac Problem.
13. Time Magazine: January 28, 1957, p. 79.
14. HAMMARSTEN, J. F., CATHEY, C. W., REDMOND, R. F. AND WOLF, S.: Serum cholesterol, diet and stress in patients with coronary artery disease. Abstract, Am. Soc. Clin. Invest. Annual Meeting May 1957.
15. GROEN, J., TJIONG, B. K., KAMMINGA, C. E., AND WILLEBRANDS, A. F.: The influence of nutrition, individuality, and some other factors, including various forms of stress, on the serum cholesterol. Voeding **13**: 556, 1952.
16. MILES, H. H. W., WALDFOGEL, S., BARRABEE, E. L. AND COBB, S.: Psychosomatic study of 46 young men with coronary artery disease. Psychosom. Med. **16**: 455, 1954.
17. BINGER, C.: On so-called psychogenic influences in essential hypertension. Psychosom. Med. **13**: 273, 1951.
18. CORVISART, J. N.: An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels. Translated by J. Gates. Boston, Bradford & Read, 1812.
19. SELYE, H.: The Stress of Life. New York, McGraw-Hill, 1956.

Yerushalmy, J. and Hilleboe, H. E.: Fat in the Diet and Mortality from Heart Disease. New York State J. Med. **57**: 2343 (July 15), 1957.

The authors evaluate the primary data of an indirect study reported in 1953 that led to the assumption of a strong association between the percentage of calories available as fat in the national diet and the national death rates from arteriosclerotic and degenerative heart disease. The apparent association is greatly reduced when tested on all countries for which data are available instead of the 6 countries used by the investigator. The presumed association is not "specific" for fat in the diet or for diseases of the heart. The suggested association between national death rates from heart disease and percentage of fat in the diet available for consumption cannot at the present time be accepted as valid. It is suggested that in indirect studies of association it is the responsibility of the investigator to report the basis on which the primary data were selected, their limitations, any qualifying conditions or considerations, and the method used for testing the validity of the results.

HARRIS

Sympathectomy for Raynaud's Phenomenon

Follow-Up Study of 70 Women with Raynaud's Disease and 54 Women with Secondary Raynaud's Phenomenon

By Ray W. Gifford, Jr., M.D., Edgar A. Hines, Jr., M.D., and Winchell McK. Craig, M.D.

Follow-up information has been obtained from 70 women with Raynaud's disease and 54 women with secondary Raynaud's phenomenon who were subjected to surgical sympathetic denervation of one extremity or more. The results of sympathectomy in the upper and lower extremities are described. The effect of operation on the subsequent course, the complications and sequelae are presented and compared with the reports of others.

GIFFORD and Hines[1] reviewed the clinical data from the records of 474 female patients who had been seen at the Mayo Clinic from 1920 through 1945 and for whom a diagnosis of Raynaud's disease had been confirmed by use of the criteria of Allen and Brown.[2, 3] Three hundred ninety-seven of these patients were treated by nonsurgical methods and the results presented. Seventy-seven women were subjected to surgical sympathetic denervation of one or more extremity. In this report the results of surgical sympathectomy are evaluated in the 70 women with Raynaud's disease in whom we have adequate follow-up information and in 54 women with secondary Raynaud's phenomenon.

Raynaud's Disease

Method of Study. The diagnosis of Raynaud's disease was established either preoperatively or postoperatively in all cases by reference to the criteria of Allen and Brown.[2, 3] Stated briefly, these criteria are (1) episodes of Raynaud's phenomenon excited by cold or emotion; (2) bilaterality of Raynaud's phenomenon; (3) absence of gangrene, or, if present, its limitation to minimal grades of cutaneous gangrene; (4) absence of any other primary disease that might be causal, such as occlusive arterial disease, acrosclerosis, cervical rib, or organic disease of the nervous system, and (5) symptoms for at least 2 years. Cases of secondary Raynaud's phenomenon were carefully excluded.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Follow-up data were obtained by questionnaire, by re-examination at the clinic, or both.

Age at Onset and Duration of Symptoms Prior to Sympathectomy. The ages at onset of Raynaud's disease as well as at time of sympathectomy of the 70 patients are given in table 1. Ninety-three per cent of the patients were less than 40 years old and 70 per cent were less than 30 years old when symptoms of Raynaud's disease were first noted. Seventy-three per cent were less than 40 years of age when sympathectomy was undertaken. The shortest duration of Raynaud's phenomenon at time of sympathectomy was 1 year for 3 patients, and the longest duration of symptoms before operation was 23 years for 1 patient. The mean duration of symptoms before operation was 7 years. Eighty-one per cent had had symptoms for 10 years or less. Six patients were operated on less than 2 years after onset of symptoms, but for all, follow-up data were more than adequate to satisfy the fifth criterion of Allen and Brown.

Location of Raynaud's Phenomenon. Raynaud's phenomenon occurred in the fingers of both hands of all 70 patients. Fifty-one patients noted vasomotor phenomena in the toes also, and the nose of one was similarly affected.

Precipitating Factors. Exposure to cold was the only precipitating factor for Raynaud's phenomenon cited by 46 women. The remaining 24 stated that emotional reactions as well as exposure to cold were responsible.

Phases of Color Change. Detailed descriptions of the phases of color change were available for only 22 patients. Seventeen had the typical 3-phase color changes (pallor to cyanosis to rubor), 4 had only 2 phases of color change, and 1 described pallor only.

TABLE 1.—*Ages of 70 Women with Surgical Treatment*

Age (years)	Patients	
	At onset of Raynaud's disease	At time of sympathectomy*
Less than 10	2	0
10–19	20	5
20–29	27	28
30–39	16	18
40–49	5	17
50–55	0	2
Total	70	70
Youngest	4	16
Oldest	42	55
Mean	25	32

* In cases in which more than one sympathectomy was done, age at time of first operation was recorded.

Family History. Only 2 patients gave a family history of Raynaud's disease.

Associated Diagnoses. Thirteen of the 70 patients were sufficiently troubled by various functional and neurotic symptoms (exclusive of migraine headache) to warrant their inclusion among the final diagnoses. Ten patients had migraine headaches, and 2 had arterial hypertension (greater than 150 mm. Hg systolic and 90 mm. Hg diastolic).

Incidence of Complications Before Operation. Only 24 (34 per cent) of the 70 women were free of the complications of Raynaud's disease before the diagnosis was first made at the clinic. Twenty-one (30 per cent) had or gave a history of trophic changes* in the fingers. One patient had trophic changes in the toes. Ten women (14 per cent) had evidence of sclerodactylia† in the fingers when sympathectomy was performed. Thirteen (19 per cent) had both trophic changes and sclerodactylia in the fingers preoperatively and 1 had trophic changes and sclerodactylia in the fingers and toes. One woman had calcinosis in the finger tips in addition to trophic lesions and sclerodactylia. A nonhealing and painful ulcer had led to amputation of the terminal phalanx of the left third finger of 1 patient before she was first seen at the clinic.

In summary, 51 per cent of the patients with Raynaud's disease had or gave a history of trophic lesions of the digits and 34 per cent had sclerodactylia. These figures include the 20 per cent who had both.

That patients with the more severe lesions were chosen for sympathectomy is amply demonstrated by comparing these figures with the incidence of initial complications among the previously reported group[1] treated conservatively. Among 307 such patients only 3 per cent had trophic changes in the digits, 7 per cent had sclerodactylia, and 2 per cent had both when the diagnosis of Raynaud's disease was first made or suspected at the clinic. Amputation of terminal phalanges of 2 toes had been necessary for 1 woman.

The mean age at onset of Raynaud's disease was lower for the surgical group (25 years) as compared to the nonsurgical group (33 years). Emotional reactions were factors in precipitating Raynaud's phenomenon in a greater percentage of the surgically treated group.

Types of Sympathectomy. Eighty-nine operations to interrupt sympathetic nervous pathways were performed on the 70 women with Raynaud's disease, and the types of procedures employed are listed in table 2. Sympathectomy was performed on 52 women for the upper extremities only, for the lower extremities only for 2 women, and for both the upper and the lower extremities for 16 women. More extensive ganglionectomy was performed on 2 women who had obtained no relief from earlier ganglionectomy. Each is included as only 1 operation in table 2. Three women underwent cervicothoracic ganglionectomy after resection of the thoracic trunk had failed to give relief. Only the final result for each patient will be included in subsequent tables. Bilateral procedures were considered and evaluated as 1 operation because in most cases the responses between paired denervated extremities did not vary appreciably.

The cervicothoracic ganglionectomy of Ad-

* By trophic changes we mean ulceration, necrosis, chronic or recurrent paronychia, scarring, and fissuring.

† For the purposes of this paper sclerodactylia will be defined as sclerodermatous changes confined to the skin of the digits. As a complication of Raynaud's disease it remains localized in the acral parts in contradistinction to the progressive scleroderma that is characteristic of acrosclerosis and diffuse scleroderma.

son[4] consists of the extirpation of the stellate ganglion and, usually but not always, of the second thoracic sympathetic ganglion through a posterior approach. It is a postganglionic sympathectomy. Resection of the thoracic trunk, proposed independently by Smithwick[5] and Telford,[6] consists of dividing the sympathetic chain between the third and fourth thoracic ganglia and dividing the rami to the second and third ganglia. The second and third thoracic nerves are divided proximal to the sensory root ganglia. No ganglia are removed and hence this is a preganglionic sympathectomy. The anterior rhizotomy performed for 1 patient was a variation of the preganglionic sympathectomy.

Duration of Follow-up after Sympathectomy. The period of postoperative follow-up for these 70 women varied from 1 to 28 years and the mean was 12 years. The mean period of follow-up after cervicothoracic sympathectomy was 11 years, and after lumbar sympathectomy 14 years.

Effect of Sympathectomy on Raynaud's Phenomenon. Forty-three (63 per cent) of the 68 patients with Raynaud's disease who underwent sympathectomy for the upper extremities noted definite lessening in the severity and frequency of Raynaud's phenomenon after operation (table 3). For 9 of these patients Raynaud's phenomenon disappeared entirely. Complications of Raynaud's disease in the form of trophic lesions of the digits or sclerodactylia or both were present preoperatively for 45 per cent of the women who obtained complete relief from Raynaud's phenomenon; complications were present preoperatively for almost 70 per cent of those who obtained only partial or no relief. There were no striking differences in the results produced by preganglionic and postganglionic procedures.

In striking contrast to the results of sympathectomy for the upper extremities are the results obtained by lumbar sympathectomy for the lower extremities. Complete and permanent relief from Raynaud's phenomenon in the feet was obtained for 83 per cent of these patients

TABLE 2.—*Types of Sympathectomy Performed on 70 Women*

Type of operation	Operations
Cervicothoracic ganglionectomy (Adson)	
unilateral	1
bilateral	53
Resection of thoracic trunk (Smithwick; Telford)	
bilateral	9
Undetermined type (performed elsewhere)	
unilateral	1
bilateral	6
Bilateral rhizotomy ($T_{2, 3, 4, 5}$)	1
Bilateral lumbar sympathectomy	18
Total	89*

* More than one operation was performed on 19 women as follows: thoracic trunk resection followed later by cervicothoracic ganglionectomy on 3; bilateral lumbar sympathectomy in addition to sympathectomy for upper extremities on 16. Ten operations were performed elsewhere.

TABLE 3.—*Effect of Sympathectomy on Raynaud's Phenomenon*

Raynaud's phenomenon after operation	Patients having extremities denervated	
	Upper	Lower
Disappeared	9	15
Improved	34	2
Same or worse	25	1
Total	68	18

TABLE 4.—*Effect of Sympathectomy on Trophic Lesions and Sclerodactylia*

Effect on lesion	Trophic lesions of patients having extremities denervated		Sclerodactylia of patients having extremities denervated	
	Upper	Lower	Upper	Lower
Present before operation				
Disappeared	13	1	5	0
Improved	8	0	8	0
Same or worse	14	0	8	0
Not present before operation				
None after operation	29	16	34	18
Appeared after operation	4	1	6	0
Total	68	18	61*	18

* Follow-up data insufficient for evaluation in 7 cases.

with Raynaud's disease and only 1 patient (6 per cent) failed to obtain any relief. Only 1 patient had complications of Raynaud's disease in the feet before operation, and she obtained an excellent result.

Effect of Sympathectomy on Trophic Lesions. Trophic lesions were present on the fingers of 35 patients with Raynaud's disease before cervicothoracic sympathectomy. Thirty-seven per cent of these women had no further difficulty with trophic lesions after operation. Sympathectomy reduced the severity and frequency of trophic lesions of 23 per cent but failed to give permanent improvement of the trophic lesions of 40 per cent (table 4).

Trophic lesions of the fingers appeared for the first time after cervicothoracic sympathectomy in 4 (12 per cent) of 33 women with Raynaud's disease. With regard to trophic lesions of the upper extremities, the results obtained by preganglionic procedures were not significantly different from those obtained by postganglionic procedures. Lumbar sympathectomy was followed by complete disappearance of trophic lesions of the toes in the only case of Raynaud's disease in which they were present preoperatively. Trophic lesions of the toes developed postoperatively in 1 of 17 women who had no such lesions preoperatively.

Effect of Sympathectomy on Sclerodactylia. Twenty-four patients with Raynaud's disease had sclerodactylia of the fingers before cervicothoracic sympathectomy was performed, but follow-up data with regard to sclerodactylia were adequate for only 21. Five (24 per cent) noted complete regression of sclerodactylia after sympathectomy, and 8 (38 per cent) noted definite improvement (table 4). Sclerodactylia was not present preoperatively on the fingers of 44 women. Postoperative follow-up data were adequate with regard to sclerodactylia for only 40 women of whom 6 (15 per cent) first noted sclerodactylia postoperatively. There was no appreciable difference between preganglionic and postganglionic procedures with regard to their effect on sclerodactylia of the upper extremities.

Sclerodactylia was not present in the toes of any patient undergoing lumbar sympathectomy either before or after operation.

Incidence of Calcinosis after Sympathectomy. Calcinosis developed postoperatively in the fingers of 5 (7 per cent) of the 68 women with Raynaud's disease who had undergone sympathectomy for the upper extremities. All 5 had trophic lesions or sclerodactylia or both preoperatively and these complications persisted in varying degrees of severity after operation. All had undergone bilateral stellate ganglionectomy, and for 4 of the 5 women the second thoracic ganglia were extirpated also. Raynaud's phenomenon failed to improve after operation for 4 of the 5 women who subsequently developed calcinosis.

The one woman who had calcinosis before sympathectomy was subjected to cervicothoracic sympathectomy (type unknown) elsewhere. The result was unsatisfactory in all respects, in that Raynaud's phenomenon, trophic lesions, sclerodactylia, and calcinosis persisted with undiminished severity.

Incidence of Amputation after Sympathectomy. Two women (3 per cent) of the 68 who underwent sympathectomy for Raynaud's disease of the upper extremities lost parts of fingers at a later time. No patient required amputation of toes after lumbar sympathectomy.

A woman, aged 27 years, had had Raynaud's phenomenon for 2 years when she was first seen at the clinic in 1944. A sweating test showed that sympathectomy performed elsewhere for the upper extremities was incomplete. Because of recurrent ulcerations of the tips of the fingers, bilateral stellate and second thoracic ganglionectomy was performed in 1944. For 2 years after operation considerable improvement in the Raynaud's phenomenon and in the recurrent ulcerations of the fingers occurred. Thereafter symptoms recurred and the patient finally lost the distal phalanx of the right second finger due to painful, infected ulcerations. Whether this phalanx was amputated or sloughed spontaneously is not clear from follow-up data.

A woman, aged 48 years, had had Raynaud's disease for 23 years before bilateral stellate ganglionectomy was performed in 1942. For 5 years after operation she was free of all symptoms including trophic lesions and scle-

rodactylia that were present initially. In 1948, infected ulcers developed at the tips of the thumb and second, third, and fourth fingers of the right hand, and sclerodactylia was again evident. A sweating test indicated complete sympathetic denervation of the upper extremities. The distal 2 phalanges of the right ring finger had to be amputated.

As mentioned previously, 1 woman, aged 21 years who had had Raynaud's disease for 3 years, had required amputation of the distal phalanx of the left third finger before coming to the clinic the first time in 1944. Bilateral stellate ganglionectomy was performed at the clinic. In the ensuing 7 years she had no further trouble with trophic lesions of the fingers and Raynaud's phenomenon was much less troublesome. Sclerodactylia was not present at any time.

Over-all Results of Sympathectomy. Heretofore the effects of sympathectomy on Raynaud's phenomenon, trophic lesions, and sclerodactylia have been considered separately. Such evaluation does not take into consideration the fact that in a single patient sympathectomy may have dissimilar effects on Raynaud's phenomenon and the pre-existing complications of Raynaud's disease. Striking improvement in only 1 category was often responsible for a greater degree of rehabilitation than moderate improvement in 2 or 3 categories. Conversely, striking improvement in nondisabling symptoms was occasionally nullified by lack of improvement in the most disabling symptom or complication. An attempt has been made, therefore, to evaluate the total result of sympathectomy for each patient individually, taking into consideration preoperative and postoperative disability according to the following criteria:

1. An excellent result indicates absolutely no disability from Raynaud's disease. To be included in this group a patient must have obtained complete and permanent relief not only from Raynaud's phenomenon but also from any preoperative complications that may have existed.

2. A good result indicates definite and often striking reduction in disability from Raynaud's disease. Many patients included in this group might well have been included in the group of excellent results had minor symptoms not persisted.

3. A fair result indicates only modest improvement with continuation or recurrence of disability after operation, although less marked than preoperatively. Usually the most disabling symptom was least improved.

4. A poor result indicates that disability continued or recurred postoperatively with unabated severity. In some cases new complications of Raynaud's disease appeared, so that disability was actually greater after operation.

TABLE 5.—*Over-All Results of Sympathectomy*

Over-all results	Patients having extremities denervated	
	Upper	Lower
Excellent	7	15
Good	30	2
Fair	6	0
Poor	25*	1
Total	68†	18

* Incomplete denervation in 4 patients indicated by sweating test.

† Two women (3 per cent) required amputation of phalanges in follow-up period.

The results of sympathectomy for Raynaud's disease according to these criteria are given in table 5. In the upper extremities sympathectomy yielded good or excellent results for 54 per cent of cases. In 4 women persistence of sweating in the hands indicated that denervation of the upper extremities was incomplete after sympathectomy and they failed to obtain relief. If these cases are excluded from the series, the proportion of patients obtaining good or excellent results is increased to 58 per cent. Good or excellent results were apparent immediately after sympathectomy, and improvement was maintained throughout the period of follow-up. However, of the 31 women for whom sympathectomy yielded a fair or poor result, the failure was apparent immediately after operation for only 8 (26 per cent). The remainder had relapses after showing considerable improvement for periods that varied from 2 months to 6 years after operation.

Only 1 patient from the group with good or excellent results was followed for less than 2 years postoperatively, and only 5 from this

group were followed for less than 5 years. The mean period of postoperative follow-up for this group was 12 years.

Good or excellent results were obtained in 65 per cent of the women without complications of Raynaud's disease before operation, whereas only 49 per cent of women with complications before operation obtained good or excellent results. Otherwise there was no correlation between preoperative data and the result obtained by sympathectomy. Specifically, the result obtained by sympathectomy in the upper extremities did not seem to be influenced by age (either at onset of the disease or at time of operation), duration of symptoms before operation, the incidence of emotional reactions as precipitating factors for the vasospastic phenomena, or the use of tobacco. Likewise, the type of sympathectomy performed seemed to have no influence on the final results.

Good or excellent results were obtained for 94 per cent of women who had lumbar sympathectomies for Raynaud's disease of the feet. Eighty-three per cent got excellent (complete and permanent) relief. Only 1 patient who had lumbar sympathectomy had complications of Raynaud's disease in the feet later.

Sixteen women had sympathectomy in both upper and lower extremities and none obtained a better result in the upper extremities than in the lower. In 11, the results in the lower extremities were better than in the upper extremities and in 5 the results in the upper and lower extremities were the same.

Fifty-two women had undergone sympathectomy for the upper extremities only. Thirty-three of these women also had Raynaud's disease of the lower extremities but not severe enough to warrant lumbar sympathectomy. After cervicothoracic sympathectomy, Raynaud's disease became more marked in the lower extremities of 7 of these 33 women, remained unchanged in 1, and improved or disappeared in 14. There was inadequate follow-up information concerning Raynaud's disease in the lower extremities in the remaining 11.

Causes of Death in Follow-up Period. Six women who had undergone sympathectomy for Raynaud's disease died during the period of follow-up. There was no operative mortality, and all deaths occurred at least 1 year after sympathectomy. One patient died of pneumonia, 1 of pulmonary tuberculosis, and 1 died suddenly after injection of a local anesthetic agent. Causes of death in the remaining 3 women were unknown. Ages at time of death varied from 30 to 52 years and averaged 39 years. All had had Raynaud's disease for at least 10 years prior to death. The sympathectomy had given good or excellent results for all except 1 of the patients who died.

Discussion

When results of this study are compared with results of previous similar investigations (table 6), it should be remembered that all of our patients were women and all had Raynaud's disease. All cases of secondary Raynaud's phenomenon were carefully separated. Previous authors have not confined their follow-up studies to women, although by the nature of the disease, the majority would be women, and some have included patients with secondary Raynaud's phenomenon and other arteriospastic diseases such as livedo reticularis and acrocyanosis. We have no reason to believe that the results of sympathectomy for Raynaud's disease would be different in male patients, but no large series is available for comparison. Apparently Raynaud's disease is not severe in men, since Hines and Christensen[14] reported that only 2 of 69 male patients with Raynaud's disease were subjected to sympathectomy. Both obtained satisfactory results.

We are in agreement with all previous authors that the results of sympathectomy for Raynaud's disease are vastly better and more predictable in the lower extremities than in the upper.

Like others, we have found a high incidence of relapse in the first few years after sympathectomy in the upper extremities. Blain and colleagues[11] observed relapse as late as 13 years after cervicothoracic sympathectomy whereas Barcroft and Hamilton,[9] and Kinmonth and Hadfield[13] stated that most failures are evident within the first year after operation. Our data indicate that most relapses occur within the first 2 years after operation, as shown by Felder and colleagues,[10] although in our study 1 re-

TABLE 6.—*Review of the Literature on Sympathectomy for Raynaud's Disease and Allied Conditions**

Author and date	Follow-up (years)	Results in per cent of cases or extremities					
		Upper extremities			Lower extremities		
		Good or excellent	Fair	Poor	Good or excellent	Fair	Poor
Telford, 1944[7]	More than 1	43	22	35	100	—	—
Haxton, 1947[8]	1–14	35	20	45	57	29	14
Barcroft and Hamilton,[9] 1948	1–6	89	—	11	—	—	—
Felder and coworkers,[10] 1949	½–20	64	—	36	70	13	17
Blain, Coller, and Carver, 1951[11]	4–15	58	—	42	100	—	—
Robertson and Smithwick,[12] 1951	5–15	45	42	13	100	—	—
Kinmonth and Hadfield,[13] 1952	1–13	69	13	18	—	—	—
Gifford, Hines, and Craig, 1957	1–28	54	9	37	94	—	6

* Some authors included a few cases of livedo reticularis, acrocyanosis, and secondary Raynaud's phenomenon.

lapse developed 6 years after cervicothoracic sympathectomy. This tendency to relapse after initial improvement must be taken into consideration in evaluating the results of sympathectomy for Raynaud's disease in the upper extremities.

Our data do not reveal any way by which the results of sympathectomy in the upper extremities can be predicted in advance, except that good or excellent results were obtained more often when complications of Raynaud's disease were not present before operation. This was also true in the series of Kinmonth and Hadfield.[13] Our conclusion that good or excellent results were obtained more often when complications of Raynaud's disease were not present before operation is of little practical importance, however, since our companion study[1] has shown that most patients with uncomplicated Raynaud's disease get along well on conservative management and surgical treatment is not usually indicated.

The data presented herein do not permit us to take sides in the controversy between the proponents of preganglionic sympathectomy[7, 12] and the proponents of postganglionic sympathectomy.[10, 11] Three women in this series who failed to obtain relief from resection of the thoracic trunk (preganglionic sympathectomy) subsequently received great benefit from cervicothoracic ganglionectomy (postganglionic). If these 3 cases are counted as failures for trunk resection and as successes for ganglionectomy, good or excellent results were obtained after 50 per cent of the latter operations and after 67 per cent of the former. The small number of trunk resections performed does not make this difference significant. Haxton[8] and Kinmonth and Hadfield[13] also found that the two types of sympathectomy give similar results. Stellate ganglionectomy alone seemed to yield good or excellent results as often as when the second thoracic ganglion was also removed. Felder and associates[10] found that the results of sympathectomy were better when the stellate ganglion was extirpated. Recently Ray[15] has suggested that a more complete sympathectomy for the upper extremity might be achieved by removing the sympathetic chain from the middle cervical ganglion to the third thoracic ganglion inclusive. There is no evidence as yet that this procedure gives better results than those obtained by the less extensive operations employed for this series.

The incidence of long-term good results of the surgical treatment of Raynaud's disease presented in this paper is not much greater than the incidence of long-term good results of conservative treatment presented in the previous study.[1] The 2 groups of patients are not strictly comparable, however, since patients with the more severe disease were more likely to be chosen for, and to accept, sympathectomy. This is ably demonstrated by the higher incidence of complications among the surgically treated group.

The early age at death of 6 patients with Raynaud's disease in this series is disturbing and raises the question of mistaken diagnoses or

untoward sequelae of cervicothoracic sympathectomy. Since the causes of death of 3 patients are not known and 64 of the 70 women were still alive at the time of last follow-up, no conclusions can be drawn as yet.

Secondary Raynaud's Phenomenon

In addition to the 70 women with Raynaud's disease, 54 women with Raynaud's phenomenon secondary to other diseases were also subjected to sympathectomy of the upper or lower extremities or both prior to 1946. The diagnoses included acrosclerosis (37 patients), rheumatoid arthritis (5 patients), livedo reticularis or acrocyanosis (5 patients), chronic occlusive arterial disease (2 patients) and chronic pernio, periarteritis nodosa, scalenus anticus syndrome, indeterminate hemorrhagic diathesis, and indeterminate disease of the central nervous system (1 patient each). Sympathectomy, although giving better results in the lower than in the upper extremities, was successful much less frequently than in primary Raynaud's disease (table 7). The majority of the good or excellent results were obtained in the patients with acrocyanosis, livedo reticularis, scalenus anticus syndrome, and chronic pernio. Sympathectomy was followed by major or minor amputations in 6 patients in this group. Nineteen (35 per cent) of the women with secondary Raynaud's phenomenon were dead at the time of follow-up. The average age at death was 39 years.

Errors in the diagnosis of Raynaud's disease will lead to disappointing results from sympathectomy since Raynaud's phenomenon secondary to other diseases (notably acrosclerosis) usually responds poorly to sympathectomy.

TABLE 7.—*Over-All Results of Sympathectomy for Secondary Raynaud's Phenomena*

Over-all results*	Patients having extremities denervated	
	Upper	Lower
Excellent	2	7
Good	7	2
Fair	4	0
Poor	33	9
Total	46*	18†

* Four patients required amputations of one or more phalanges after sympathectomy and one patient required amputation of an arm.

† One patient required amputation of both legs after lumbar sympathectomy.

Summary

Sympathectomy for Raynaud's disease affecting the upper extremities gave good or excellent results in 37 (54 per cent) of 68 women in this series. Good or excellent results were obtained more frequently if complications of Raynaud's disease (trophic lesions or sclerodactylia or both) were not present before operation. There was no significant difference between the results obtained by preganglionic and postganglionic sympathectomies. Two (3 per cent) of the 68 patients lost portions of fingers after sympathectomy. Of the patients who had a fair or poor long-term result, the majority initially obtained a good result and then had relapses during the first 2 years after sympathectomy.

Sympathectomy for the lower extremities gave good or excellent results for 17 (94 per cent) of 18 women with Raynaud's disease. Sympathectomy for Raynaud's phenomenon secondary to other diseases gave poor results in the upper extremities in 72 per cent of cases and only slightly better results in the lower extremities.

Sympathectomy should be reserved for patients with the more severe and progressive Raynaud's disease, since the prognosis is good without sympathectomy when the disease is mild or moderately severe, and not progressing.

Summario in Interlingua

Sympathectomia in le tractamento de morbo de Raynaud afficiente le extremitates superior produceva bon o excellente resultatos in 37 ex le 68 feminas del presente serie (54 pro cento). Bon o excellente resultatos esseva obtenite plus frequentemente quando complicationes de morbo de Raynaud—lesiones trophic o sclerodactylia o ambes—non esseva presente ante le operation. Nulle significative differentia esseva notate inter le resultatos obtenite per sympathectomia preganglionic e le resultatos obtenite per sympathectomia postganglionic. Duo del 68 patientes (3 pro cento) perdiva partes de digito post sympathectomia. Quanto al patientes in qui le resultatos a longe vista esseva solmente acceptabile o clarmente mal,

le majoritate de illes comenciava per monstrar bon resultatos sed habeva recidivas durante le prime 2 annos post le sympathectomia.

Sympathectomia pro morbo de Raynaud in le extremitates inferior produceva bon o excellente resultatos in 17 ex 18 feminas (94 pro cento).

Sympathectomia pro phenomeno de Raynaud secundari a altere morbos produceva mal resultatos in 72 pro cento del casos in que le extremitates superior esseva afficite e resultatos non multo melior in le casos in que le extremitates inferior esseva afficite.

Sympathectomia debe esser reservate pro patientes con morbo de Raynaud in forma sever e progressive, proque le prognose es bon sin sympathectomia quando le morbo es leve o moderatemente sever e non progredente.

REFERENCES

[1] GIFFORD, R. W., JR., AND HINES, E. A. JR.: Raynaud's disease among women and girls. Circulation **16:** 1012, 1957.

[2] ALLEN, E. V., AND BROWN, G. E.: Raynaud's disease: A critical review of minimal requisites for diagnosis. Am. J. M. Sc. **183:** 187, 1932.

[3] — AND —: Raynaud's disease affecting men. Ann. Int. Med. **5:** 1384, 1932.

[4] ADSON, A. W.: Changes in technique of cervicothoracic ganglionectomy and trunk resection. Am. J. Surg. n.s. **23:** 287, 1934.

[5] SMITHWICK, R. H.: Modified dorsal sympathectomy for vascular spasm (Raynaud's disease) of the upper extremity: A preliminary report. Ann. Surg. **104:** 339, 1936.

[6] TELFORD, E. D.: The technique of sympathectomy. Brit. J. Surg. **23:** 448, 1935.

[7] —: Discussion on peripheral vascular lesions. Proc. Roy. Soc. Med. **37:** 621, 1944.

[8] HAXTON, H. A.: Regeneration after sympathectomy and its effects on Raynaud's disease. Brit. J. Surg. **35:** 69, 1947.

[9] BARCROFT, H., AND HAMILTON, G. T. C.: Results of sympathectomy of the upper limb: With special reference to Raynaud's disease. Lancet **1:** 441, 1948.

[10] FELDER, D. A., SIMEONE, F. A., LINTON, R. R., AND WELCH, C. E.: Evaluation of sympathetic neurectomy in Raynaud's disease: Based on a follow-up study of forty patients. Surgery **25:** 1014, 1949.

[11] BLAIN, A., III, COLLER, F. A., AND CARVER, G. B.: Raynaud's disease: A study of criteria for prognosis. Surgery **29:** 387, 1951.

[12] ROBERTSON, C. W., AND SMITHWICK, R. H.: The recurrence of vasoconstrictor activity after limb sympathectomy in Raynaud's disease and allied vasomotor states. New England J. Med. **245:** 317, 1951.

[13] KINMONTH, J. B., AND HADFIELD, G. J.: Sympathectomy for Raynaud's disease: Results of ganglionectomy and preganglionic section compared. Brit. M. J. **1:** 1377, 1952.

[14] HINES, E. A., JR., AND CHRISTENSEN, N. A.: Raynaud's disease among men. J. A. M. A. **129:** 1, 1945.

[15] RAY, B. S.: Sympathectomy of upper extremity; evaluation of surgical methods. J. Neurosurg. **10:** 624, 1953.

But these sufferings are not at all necessary; they are the effects of our inexperience, and would in similar circumstances, more or less attend the exhibition of almost every active and powerful medicine we use.—WILLIAM WITHERING. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Predictive Value of Lipoprotein and Cholesterol Determinations in Diabetic Patients who Developed Cardiovascular Complications

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With the statistical assistance of Zdenek Hrubec, A.B.

A follow-up study was performed on 690 white diabetic patients 2 to 5 years after their blood had been analyzed for lipoprotein and cholesterol to determine if these lipid measures had any predictive value for development of future cardiovascular complications. The work was done in parallel to the national project in which 15,000 normal persons were followed for 1 to 2 years.[5]

IN RECENT years clinicians have searched for a laboratory test that would give predictive information and help in their treatment of the patient with atherosclerosis. The literature[1, 2] has indicated that atherosclerosis is frequently associated with elevated blood cholesterol levels. In general, however, cholesterol determinations, cholesterol/phospholipid ratios and other laboratory tests have been of questionable value in predicting the course of the disease.

BACKGROUND AND PURPOSE OF STUDY

In 1950 Gofman and his colleagues[3] stimulated a renewed interest in the relationship between atherosclerosis and blood β-lipoprotein by the use of the ultracentrifuge.[4] The U. S. Public Health Service became interested in their work and, under the National Advisory Heart Council, sponsored a joint project of 4 laboratories. The California group, the Harvard group, the Pittsburgh group, and the Cleveland Clinic group participated under the coordination of Dr. J. Franklin Yeager of the National Heart Institute. They studied the blood lipoprotein and cholesterol determinations of 15,000 normal individuals and later did a 1- to 2-year follow-up on the 4,941 males whose ages ranged from 40 to 59. In 1956 they reported on the predictability of the 65 men in the latter group who had developed coronary disease.[5]

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† Deceased March, 1954.

The Committee on Lipoproteins and Atherosclerosis had 5 objectives. The fifth one was "to relate the S_f 12–20 fraction and total cholesterol not only in normals and myocardial infarction patients but also in hypertensives and diabetics especially in patients that develop myocardial infarction."

Between 1951 and 1953 we studied 901 diabetic patients clinically as the first part of this objective.[6] Their blood serum was analyzed for lipoproteins and cholesterol in the laboratory of Dr. Max Lauffer and Dr. Martin Hanig of the Biophysics Department of the University of Pittsburgh. The findings for the males were not conclusive, but the diabetic females did show some elevation of the means for the S_f 12–20, S_f 20–100, and cholesterol values with the presence of diabetic retinopathy, atherosclerotic complications, hypertension, and blood vessel calcification. Both sexes showed significant elevation of mean lipid values with Kimmelsteil-Wilson syndrome.

This report deals with the other part of the fifth objective and is a follow-up of the original 901 diabetic patients. Only the 690 white diabetic patients are included here. It was hoped that one or a combination of the lipid measures might be found that would predict forthcoming complications in diabetic patients.

In general, if atheroma occurs in one vessel of the body, it will also be present in other areas. Warren[7] has emphasized that there is frequently a parallelism between the severity of lesions in the aortic trunk, and the coronary and cerebral vessels. For this study, new occurrences of myocardial infarction, angina pectoris, arteriosclerosis obliterans, or a cerebral

vascular accident were included and grouped as cardiovascular complications. The various atherosclerotic complications were combined in order to obtain a group useful for statistical analysis.

Methods

The follow-up study was carried out between April 1955 and October 1956. In general, 2 to 5 years had elapsed since the original examinations, as some patients were seen as early as May 1951 and a few as late as November 1953.

The 690 patients included both the private patients of the authors and Dr. Louis Pennock, and the diabetic patients in the out-patient department of the University of Pittsburgh School of Medicine.

It was possible to obtain a follow-up history and thorough physical examination on 430 patients. Emphasis was placed on weight, blood pressure, funduscopic examination, and the cardiovascular system. Information on the remaining patients was obtained in various ways; 39 patients were interviewed by telephone, 37 cases were followed from death certificates, 45 cases were reviewed from autopsy reports and hospital records, and cooperative physicians sent in reports on another 55 patients. By these methods usable information was obtained for 176 patients making a total of 606 or 87 per cent completeness of the follow-up. Our inability to follow-up 84 of the patients was mainly due to their failure to notify the post office of change of address, women changing their names through marriage, inability of neighbors to give information to the social workers making an inquiry, and uncooperative patients. The obituary file of the State of Pennsylvania was searched for all patients who could not be reached, and it may be assumed that the majority of patients for whom death certificates were not secured are probably alive. Eight of the patients with no follow-up information had cardiovascular disease at the time of the original examination. Of the males 13.8 per cent and of the females 11.2 per cent were not followed. The age distribution of the group not followed and of all the patients appears comparable.

Since we were interested in finding the number of new cardiovascular complications, a great effort was made to get as complete a description as possible of objective findings, laboratory tests, x-rays, electrocardiograms, and an impression as to the certainty of diagnosis. In the cases where sudden death occurred, preceded by angina pectoris, the patients were placed in the myocardial infarction group. However, without angina they were considered as deaths from other causes. In general, we strived as much as possible to classify patients as having new cardiovascular events only if we were reasonably sure of the diagnosis, and if the complication had not been present at the original examination.

By definition, cardiovascular complications consisted of (1) myocardial infarction, (2) angina pectoris, (3) cerebral vascular accident, and (4) arteriosclerosis obliterans. In the cases where 2 of these complications were present, the patients were included in the group designated by the lower number. Thus a patient with (1) myocardial infarction and (4) arteriosclerosis obliterans would be categorized as (1) or myocardial infarction.

Statistics having or approximating Student's t distribution were used in order to evaluate the effect of sampling variation on the differences between the patients who did and did not develop complications. Two hypotheses were tested. One was that the elevation of the mean lipid measure of the patients who developed complications is no greater than could be expected by chance. The second hypothesis was that when we divide the patients into 2 groups—with lipid values above and below the median—the difference in the proportions of complications in these 2 groups is no greater than could be expected on the basis of sampling variation.

Results

Of the 606 white patients on which the follow-up data were available, 111 died of vascular complications or multiple other causes, and 39 developed new atherosclerotic events and lived. Table 1 summarizes these regardless of their age.

Table 2 categorizes patients by sex, the number and per cent of new cardiovascular complications, and the number that died of the complication.

Of the 188 male patients, 21 developed cardiovascular complications giving an 11.2 per cent morbidity rate. Of the 331 females, 40 developed new cardiovascular complications giving a morbidity rate of 12 per cent. Of the

Table 1.—*Causes of Death and Vascular Complications*

Dead, cause	Number of patients	Living, complications	Number of patients
Myocardial infarction	32	Myocardial infarction	8
Cerebral vascular accident	16	Angina pectoris	14
Arteriosclerosis obliterans with gangrene	1	Cerebral vascular accident	10
Other causes	62	Arteriosclerosis obliterans	7
Total	111		39

TABLE 2.—*Number and Per Cent of New Cardiovascular Complications and the Number of Deaths from the Complications by Sex**

Complication	Number who developed complication	Per cent who developed complication	Number who died
White male—188 followed-up			
Myocardial infarction	9	4.8	5
Angina pectoris	4	2.1	0
Cerebral vascular accident	5	2.6	5
Arteriosclerosis obliterans	3	1.6	0
White female—331 followed-up			
Myocardial infarction	13	3.9	11
Angina pectoris	9	2.7	0
Cerebral vascular accident	14	4.2	7
Arteriosclerosis obliterans	4	1.2	1

* Percentages are based only on the number of patients who were free of complications on the original examination.

entire series of 519 patients, there was a total of 61 new cardiovascular complications, giving an over all morbidity rate of 11.8 per cent. These morbidity rates do not take into consideration variations in the duration in the time of follow-up.

In the first part of the analysis the means of the 3 lipid measures of the 61 diabetic patients who developed new cardiovascular complications are compared with the means of patients who had previous cardiovascular complications, the patients who did not develop new complications, and those whom we were unable to contact. The results for the white patients by sex are shown in table 3 and table 4 and are presented by age groups. Age has to be taken into account because, as would be expected, the older ages show a greater incidence of vascular complications, and the age group 40 to 59 is comparable to the national study.

The means for both the males and females, for all ages combined, show a lipid elevation in the group who developed complications. To understand the nature of these differences it is best to examine the relationship by age groups. As can be seen in table 3, the mean cholesterol values for male patients with new complications are higher for all ages. The difference in the 40- to 59-year age group is significant at the 5 per cent level as determined by the t test.

The means for the S_f 12–20 and S_f 20–100 measures for the patients with complications were higher in the youngest and oldest age groups but, because of the small number of patients in the youngest age group, emphasis can only be placed on the findings of the male patients 60 years and older. In the latter group the differences in all 3 measures are of borderline significance when the measures are compared singly. Since they all show the same trend of elevations of the mean values with complications, it is not likely that such consistency would result from sampling variations. It should be noted that in the males, ages 40 to 59, the mean values for the S_f 12–20 and S_f 20–100 are lower in the group with complications.

As can be seen in table 4 for the females, the mean values by age groups show elevation for all measures with 2 exceptions. One occurs in the 14 to 39 year age group, where the S_f 20–100 is higher in the diabetic patients with no complications, but this is a negligible group of 2 patients. The other exception occurs in the 60 and over age group where the cholesterol values are almost the same in the females with and without complications. The females with complications in the ages 40 to 59 show a significant elevation for all 3 measures at the 1 per cent level.

In drawing any specific conclusions from these data, it should be remembered that because of the large variability of the measurements the examination of differences between means tells nothing definite concerning a lipid determination for a *single individual*. In order to analyze the data more effectively, therefore, the percentage of patients with cardiovascular complications in each quartile of the distribution of the lipid measure was also examined.*

The results for the white males and females by age groups may be seen in table 5. In examining them it may be seen that the number of new cardiovascular events may vary from one measure to another. This is due to an occasional lipid value not being available.

* Since the patients lost in the follow-up have a tendency to somewhat lower the lipid values, the effect of excluding this group was evaluated. The quartile values were not essentially changed when these patients were included.

TABLE 3.—*Mean Cholesterol, S_f 12-20, and S_f 20-100 Values in White Males*

Classification	Age	Number of patients	Cholesterol	S_f 12-20	S_f 20-100
Atherosclerotic complications present on initial examination	14-39	0	—	—	—
	40-59	14	272.1	48.1	70.2
	60 and over	29	256.0	45.2	85.5
Total		43	261.2	46.1	80.5
No atherosclerotic complications on initial examination, but present in follow-up	14-39	2	335.5	161.0	170.0
	40-59	10	285.0	42.2	68.0
	60 and over	9	263.4	59.0	129.3
Total		21	280.6	60.7	104.0
No evidence of atherosclerotic complication on initial or follow-up examination	14-39	42	231.8	44.2	92.7
	40-59	76	240.2	42.4	88.6
	60 and over	49	235.6	42.2	75.1
Total		167	236.7	42.8	85.7
Patients unable to be followed		37	254.1	42.8	86.4

TABLE 4.—*Mean Cholesterol, S_f 12-20, and S_f 20-100 Values in White Females*

Classification	Age	Number of patients	Cholesterol	S_f 12-20	S_f 20-100
Atherosclerotic complication present on initial examination	14-39	0	—	—	—
	40-59	12	295.6	59.7	108.4
	60 and over	32	282.0	66.0	107.3
Total		44	285.7	64.3	107.6
No atherosclerotic complications at initial examination, but present in follow-up	14-39	2	448.5	79.0	45.0
	40-59	9	334.3	164.8	220.0
	60 and over	29	262.4	56.9	98.4
Total		40	287.9	82.3	123.1
No evidence of atherosclerotic complications on initial or follow-up examination	14-39	37	223.2	34.0	49.9
	40-59	116	266.0	52.5	85.7
	60 and over	138	268.3	53.5	83.5
Total		291	261.6	50.6	80.1
Patients unable to be followed		47	256.9	52.5	84.3

In the males the measures show no consistent pattern in the age groups 14 to 39 and 40 to 59. In the group 60 and over, as was the case with the mean lipid values, however there is a positive relationship between lipid values and new cardiovascular complications.

The most striking and significant results are once again in the females age 40 to 59. In this group more than 85 per cent of the vascular complications occurred in patients who had higher than median values in the original examination. A similar situation exists in the age group 14 to 39, but because of the small number no conclusion can be drawn for this group.

Kimmelsteil-Wilson Syndrome

Of the original 690 patients there were 21 cases of Kimmelsteil-Wilson syndrome. The follow-up disclosed that 16 of them had died; 4 of myocardial infarction, 2 of cerebral vascular accident, and 10 with uremia.

Hypertension

The number of patients who were not hypertensive at their original examination but

TABLE 5.—*The Number of New Cardiovascular Complications by Sex and Age Groups as Categorized According to Quartile Values of Cholesterol, S_f 12–20, and S_f 20–100*

	Cholesterol (mg. %)	Number of patients with complications	S_f 12–20 (mg.%)	Number of patients with complications	S_f 20–100 (mg. %)	Number of patients with complications
Males						
Age 14–39 (44 patients)						
Highest value	470	1	280	1	452	1
Third quartile	263	0	56	1	104	0
Second quartile	217	1	37	0	72	0
First quartile	194	0	29	0	51	1
Lowest value	139		12		15	
Age 40–59 (85 patients)						
Highest value	383	5	85	2	466	2
Third quartile	280	2	54	3	107	1
Second quartile	243	1	39	3	71	3
First quartile	210	1	28	2	45	3
Lowest value	71		14		5	
Age 60 & over (60 patients)						
Highest value	386	3	115	5	412	3
Third quartile	278	3	54	1	97	4
Second quartile	228	2	37	0	62	0
First quartile	200	0	28	3	40	1
Lowest value	147		16		5	
Females						
Age 14–39 (39 patients)						
Highest value	536	2	109	2	146	1
Third quartile	255	0	46	0	77	0
Second quartile	224	0	25	0	46	0
First quartile	200	0	24	0	22	1
Lowest value	154		4		2	
Age 40–59 (125 patients)						
Highest value	707	4	500	9	500	6
Third quartile	297	3	73	0	125	2
Second quartile	262	2	47	0	74	1
First quartile	230	0	33	0	44	0
Lowest value	162		8		4	
Age 60 & over (161 patients)						
Highest value	569	7	290	10	335	7
Third quartile	298	7	65	5	107	7
Second quartile	265	8	48	4	71	8
First quartile	220	6	36	10	48	7
Lowest value	117		11		4	

became hypertensive in the ensuing time of the follow-up were also examined in terms of lipid values. There were 15 males and 29 females in this category. No relationship was found between the original lipid measures and subsequent development of a blood pressure of 140/90 or higher.

DISCUSSION

The clinician is always looking for a laboratory test that will help him prognosticate an atherosclerotic complication. For this reason, a 2- to 5-year follow-up of 690 white diabetic patients was carried out and the data on ensuing complications were analyzed.

This study paralleled the one on 4,941 normal persons[5] in which 65 myocardial infarctions or their equivalent occurred during a 2-year period.

As can be seen from the preceding results, the predictability by either means or quartiles for the diabetic group as a whole is limited. Only for females between ages 40 to 59 and males 60 years or over were the mean values higher in those who developed complications than in patients who did not develop complications. In the same groups the number of complications in patients with lipid values above the upper quartile and above the median is also disproportionately higher.

In interpreting these differences it has to be remembered that the standard deviations for the group are large and that there was in Pittsburgh a small technical error of 5.5 mg. per cent for the S_f 12–20 and 5.0 mg. per cent for the cholesterol measurement of aliquots of the same blood. The 3 lipid values vary considerably from one patient to another and the low correlation of each measure with the others can be seen in table 6. With these low correlations it was decided not to combine the measures in any additive fashion, as difference between the 3 measures would not then be detected. It is possible, however, that predictability could be improved by using such a combination.

To determine if any individual lipid determination has any clinical predictive value it should be known what repeated analyses from week to week and month to month in the same

TABLE 6.—*Product Moment Correlation Coefficient between Lipid Measures*

	Male		Female	
	S_f 12–20	S_f 20–100	S_f 12–20	S_f 20–100
Cholesterol	.45	.15	.52	.30
S_f 12–20	—	.42	—	.68

individual would show. To our knowledge this has never been done, but the Donner Laboratory did do repeated studies at intervals of 1 and 2 years in a group of Framingham subjects. Large differences between the repeated measures were found except in one third of the cases where the differences in the S_f 12–20 values were less than 10 mg. per cent. Thus a single lipoprotein or cholesterol value for one individual might mean little, as it is not known if repeated determinations would be consistent over a short period of time.

Diabetes is an accelerator of atherogenesis and the lipid value may vary depending upon the degree of clinical control. In acidosis there is an elevation of cholesterol values, which fall to near normal as the diabetes comes under control. Mann[8] has shown that the lipoproteins act similarly to the cholesterol during acidosis, and with the return of control the values fall to normal. None of the patients in this study was in coma and very few had acetonuria, so it was believed that the cholesterol and lipoprotein changes in acidosis should not affect these data.

In reviewing the results presented, there is little question that atherosclerosis as manifested by clinical signs of atherosclerotic complications is associated with lipid metabolism and that there is some predictive value in the 3 lipid measures examined. The major question, however, is, from a given value, how predictable is a cardiovascular complication? If by prediction is meant the fate of an individual patient, then none of these measures would be satisfactory, as can be seen from a follow-up of this length of time. The measures are more useful for group prediction or in evaluating the chance that a patient with a high value compared to a patient with a low value will develop complications. This can be stated more definitively for the diabetic male patients 60 years or older and the female patients age 40 to 59. If the reading of a patient in these age groups is above the median value he has a 2 to 9 times greater chance of a complication occurring in the next few years. On the basis of lipid determinations however, no one can say *which individual* in the group over the fiftieth percentile will be the unfortunate patient. An inspection of table 5 shows that for all ages combined, more than 33 per cent of the new events fall above the seventy-fifth percentile for all measures.

In the national study on white males ages 40 to 59, the data were analyzed somewhat differently by the California group as compared to the other 3 laboratories. Gofman used the "atherosclerotic index or A.I." and the "standard S_f measurements." In this study we had available only the cholesterol, S_f 12–20, and S_f 20–100, so that the A.I. index could not be applied to determine predictability. In general, our results and conclusions are similar to the Pittsburgh, Harvard, and Cleveland Clinic laboratories.

The National Study[5] found 65 "major" coronary artery events in 4,941 supposedly normal patients, or a morbidity rate of 1.3 per cent. We reviewed our 61 cardiovascular complications and removed all cases that were not comparable to those in the national study. We also eliminated those patients who developed a myocardial infarction or angina pectoris in the period over 2 years after the blood specimen was taken. The 5 remaining patients of the 100 white male diabetic subjects between the ages of 40 to 59 represent a morbidity rate of 5 per cent, which is 4 times the rate observed nationally in normal persons. This is as would be expected, in that coronary artery disease is more prevalent in the diabetic. Root and co-workers[9] compared 349 diabetic to 3,400 nondiabetic subjects and found that coronary occlusion was 4 times as common in the diabetic as the nondiabetic subject in the age group 40 to 60. The mean value for these 5 patients was: cholesterol, 298.5 mg. per cent; S_f 12–20, 43.4 mg. per cent; and S_f 20–100, 48.5 mg. per cent. These values are not very different from those for the same age group with new complications shown in table 3.

The cholesterol values in this very small and possibly insignificant group of 5 patients once again emphasize what was seen in the larger groups in this study. As a predictive measurement the cholesterol value is as good as, if not better than, the lipoprotein values. The laboratory determination of cholesterol is easily performed in comparison to the analyses of the lipoproteins, which are not only complicated but require an extensively trained staff and expensive equipment.

Summary

This paper represents a part of the U. S. Public Health Service research project that was designed to determine if the lipoprotein molecule and cholesterol determinations have any predictive value for ensuing atherosclerotic complications.

There were 690 white diabetic patients examined from 1951 to 1953, and for 606 of these we were able to get follow-up data in the subsequent 2 to 5 years. In the group followed there were 61 new atherosclerotic events consisting of myocardial infarction, angina pectoris, arteriosclerotic obliterans, and cerebral vascular accidents.

The mean lipid values in the patients with complications were elevated and sometimes significantly elevated as compared to those who did not develop complications. This was most evident in the females age 40 to 59 and to a lesser extent in the males 60 and over.

When the analysis was performed by quartiles, more than 50 per cent of the complications occurred in patients whose lipid determinations were above the median. These differences were significant for the males 60 and over and for females 40 to 59. In the age group 14 to 39 there were only 2 males and and 2 females who developed complications, and no definite conclusions can be drawn even though the results appear favorable.

The lipid measures as a predictor of vascular complications in diabetic patients are not applicable to any one individual. For a large group the patients with higher values, however, tend to have a greater number of complications. The increased chance of developing a complication varies with age, sex, and the particular lipid measure.

The cholesterol value as a predictor is as good as, if not better than, the lipoprotein molecules and the complexity and expensiveness of the S_f molecule determination make its use impractical for clinical purposes.

Summario in Interlingua

Iste reporto representa parte de un projecto recercatori del Statounitese Servicio de Sanitate Public, interprendite pro determinar si mesurationes de lipoproteina e de cholesterol es de valor in predicer subsequente complicationes atherosclerotic.

Inter 1951 e 1953, 690 diabeticos blanc esseva examinate. Pro 606 de illes il esseva possibile obtener datos de observation consecutori colligite in le curso del subsequente 2 a 5 annos.

Le gruppo a observationes ulterior produceva un total de 61 nove evenimentos atherosclerotic. Istos consisteva de infarcimentos myocardial, casos de angina de pectore, casos de arteriosclerosis oblitterante, e accidentes cerebro-vascular.

Le valores medie de lipido in le patientes con complicationes esseva elevate—in certe casos a grados significative—in comparation con le valores ab patientes qui non disveloppava complicationes. Iste facto esseva le plus evidente in femininas con etates de inter 40 e 59 annos e, minus pronunciatemente, in masculos con etates de 60 annos e plus.

Quando le analyse esseva facite per quartiles, plus que 50 pro cento del complicationes occurreva in patientes in qui le valores de lipido excedeva le valor median. Iste differentias esseva statisticamente significative pro masculos de etates de 60 annos e plus e pro femininas con etates de inter 40 e 59 annos. Le gruppo de etates de inter 14 e 39 annos includeva solmente 2 masculos e 2 femininas qui disveloppava complicationes. Super iste base nulle conclusiones definite pote esser formulate, ben que le resultatos pare esser favorabile.

Le mesuration de lipido como predictor de complicationes vascular in patientes diabetic non es applicabile al caso individual. Tamen,

quando un gruppo plus extense de patientes es considerate, le patientes qui exhibi plus alte valores tende a disveloppar plus numerose complicationes. Le augmentate risco del disveloppamento de complicationes varia con le etate e le sexo del patiente e con le mesura de lipido obtenite in ille.

Le valor de cholesterol como predictor de complicationes equivale o mesmo excelle le correspondente determinationes de moleculas lipoproteinic. In plus, le complexitate e le costo del determination de moleculas lipoproteinic rende iste technica impractic pro objectivos clinic.

REFERENCES

[1] MORRISON, L., HALL, L., AND CHENEY, A.: Cholesterol metabolism. Am. J. M. Sc. **216:** 32, 1948.

[2] GERTLER, M., GARN, S., AND LERMAN, J.: Interrelationship of serum cholesterol, cholesterol esters, and phospholipids in health and in coronary artery disease. Circulation **2:** 205, 1950.

[3] GOFMAN, J. W., LINDGREN, F., ELLIOT, H., MANTZ, W., HEWITT, J., STRISOWER, S., AND HERRING, V.: Role of lipids and lipoproteins in atherosclerosis. Science **111:** 166; 186, 1950.

[4] MACINNES, P. A.: Introduction to the conference on the ultracentrifuge. Ann. New York Acad. Sc. **43:** 175, 1942.

[5] GOFMAN, J. W., ET AL.: Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Circulation **14:** 691, 1956.

[6] LOWY, A. D., JR., BARACH, J. H., AND HRUBEC, Z.: A study of lipoprotein molecules and cholesterol determinations in 901 diabetics. Diabetes **6:** 342, 1957.

[7] WARREN, S.: Pathology of Diabetes Mellitus. Ed. 2. Philadelphia, Lea and Febiger, 1938, p. 121.

[8] MANN, G. V.: Metabolism of the serum lipids in diabetes and arteriosclerosis. Diabetes **4:** 273, 1955.

[9] ROOT, H. F., BLAND, E. F., GORDON, W. H., AND WHITE, P. D.: Coronary atherosclerosis in diabetes mellitus: A postmortem study. J.A.M.A. **113:** 27, 1939.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Buerger's Disease. Leo Buerger's (b. 1879) first description appeared in the *American Journal of the Medical Sciences*, new series, 136: 567–580 (October), 1908, under the title "Thrombo-angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene."

"The disease occurs frequently, although not exclusively, among the Polish and Russian Jews, . . . We usually find it occurring in young adults. . . . After longer or shorter periods characterized by pain, coldness of the feet, ischemia, intermittent claudication, and erythromelalgic symptoms, evidences of trophic disturbances appear which finally pass over into a condition of dry gangrene. . . . I have come to the conclusion that we are dealing here with a thrombotic process in the arteries and veins followed by organization and canalization, and not with an obliterating endarteritis. . . . I would suggest that the names '*endarteritis obliterans*' and '*arteriosclerotic gangrene*' be discarded in this connection, and that we adopt the terms '*obliterating thrombo-angiitis*' *of the lower extremities* when we wish to speak of the disease under discussion."

Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris

Comparison of Six Preparations and Four Routes of Administration

By JOSEPH E. F. RISEMAN, M.D., GEORGE E. ALTMAN, M.D., AND SIDNEY KORETSKY, M.D.

The close chemical relationship between glyceryl trinitrate and erythrol tetranitrate suggests that these 2 drugs, despite clinical evidence to the contrary, should be equally effective in preventing attacks of angina pectoris. This proved to be true when the drugs were administered by the same route. Thus, erythrol tetranitrate when administered sublingually (instead of being swallowed, as is the custom) behaves like nitroglycerin and is one of the most effective vasodilators available. Conversely, nitroglycerin when swallowed (instead of being taken sublingually, as is the custom) is ineffective and erratic in activity. A similar striking increase in vasodilating action on sublingual administration is seen also with mannitol hexanitrate and triethanolamine trinitrate and to a lesser extent with pentaerythritol tetranitrate but not with sodium nitrite.

The prolonged effect of erythrol tetranitrate, when administered sublingually or in the buccal pouch, makes it particularly valuable in the clinical management of patients with angina pectoris.

OF ALL the drugs available for preventing attacks of angina pectoris nitroglycerin, amyl nitrite, and octyl nitrite are by far the most effective. Of these 3, nitroglycerin is the most widely used, primarily because of its definite dosage, simplicity of administration, and low cost. The one drawback to its clinical usefulness is the short duration of action. Measurements in this laboratory[1] demonstrated that, although the prophylactic benefit of sublingual nitroglycerin may persist for an hour in some patients, its action persists for minutes only in most patients. Similar studies with other drugs[1-6] showed that nitroglycerin is of prophylactic benefit to more patients and to a greater degree than any other medication. The present report is concerned with a search for drugs as effective as nitroglycerin, but with more prolonged activity.

The graphic chemical formulas of the 6 nitrites studied in the present series are shown in figure 1. If the action of nitroglycerin is due to the presence of $-ONO_2$ groups, all 6 should have therapeutic value in angina pectoris.

Two problems were of particular interest. First, since the chemical structures of nitroglycerin and erythrol tetranitrate are similar, why is the former much more effective for preventing attacks of angina pectoris? Second, since laboratory studies show that sodium nitrite has a highly effective vasodilating action, why is this drug of such limited clinical value in treating angina pectoris? A study of the extensive literature suggests that part of the difference in clinical effectiveness of these 6 drugs may be due to the various routes of administration employed.

Nitroglycerin or *glycerol trinitrate* is an oily liquid and, originally, was used in alcoholic solution, i.e., tincture glanoin. The vivid description by Field in 1858[7] showed that this solution, when dropped on the tongue, was readily absorbed by the mucous membranes of the mouth with striking effects. One of the patients treated by Field may well have suffered from angina pectoris, but Murrell[8] is generally given credit for first advocating the

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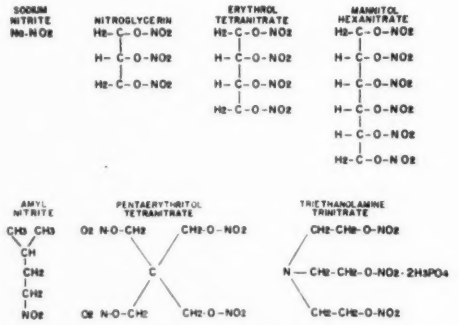

FIG. 1. Graphic chemical formulas of amyl nitrite and the 6 nitrites studied in the present series.

use of nitroglycerin (1879) for the treatment of this condition. Murrell prescribed 10 minims of a 1 per cent solution of nitroglycerin in water to be swallowed several times daily. Although in the past[9] there was some difference of opinion as to the best route of administration, nitroglycerin has been usually prescribed for sublingual use.

Recently, a slow release preparation for oral use was made available. This material (Nitroglyn) is a porous plastic tablet impregnated with nitroglycerin, designed so that the drug leaches out of the matrix slowly; thus, swallowing a single tablet makes the medication available to the patient for several hours. Few evaluations of the effectiveness of Nitroglyn are available. Russek et al.[10] found it of little value in correcting the exercise electrocardiogram although Huppert and Boyd[11] reported that its use decreased the necessity for nitroglycerin in 16 out of 25 patients.

Nitroglycerin is readily absorbed from the skin.[12, 13] An ointment containing nitroglycerin has recently been made available commercially for the treatment of peripheral vascular disease. This preparation has been used with some clinical success in some patients with angina pectoris.[14, 15]

Erythrol tetranitrate, according to the graphic formula, should be an ideal drug because it is identical with glycerol trinitrate except that its molecule is ⅓ larger; this might well prolong its activity without detracting from its effectiveness. Bradbury's early studies[16] and also subsequent measurements[17-19] showed that both drugs are effective in lowering the blood pressure of laboratory animals but erythrol tetranitrate has a more prolonged action. However, exercise tolerance and electrocardiographic measurements[4, 6, 20] showed that although erythrol tetranitrate is of some prophylactic value in some patients with angina pectoris, it is considerably less effective than nitroglycerin, both in the degree to which the exercise tolerance is increased and in the number of patients benefited.

One possible reason for this discrepancy might lie in the different routes of administration used with these 2 drugs. Erythrol tetranitrate is a solid and hence, unlike nitroglycerin, is administered in tablets to be swallowed. In studying the comparative value of the different nitrites, therefore, it is necessary to compare the effect of oral, sublingual, and parenteral administration.

Mannitol hexanitrate resembles glycerol trinitrate and erythrol tetranitrate in that it is prepared by nitration of a straight chain alcohol; in this instance the alcohol contains 6 carbon atoms and the nitrate contains 6 $-ONO_2$ groups. Mannitol hexanitrate, like erythrol tetranitrate and the other compounds to be described, is a solid and is prescribed to be swallowed. Studies in this laboratory[5, 21] indicated that mannitol hexanitrate when given in this manner is only of moderate benefit to patients with angina pectoris.

Pentaerythritol tetranitrate like erythrol tetranitrate, has 4 $-ONO_2$ groups; the structural configuration and physical characteristics of pentaerythritol tetranitrate, however, are quite different from those of erythrol tetranitrate or nitroglycerin.[12, 13]

This drug has been the subject of a number of clinical investigations. The purely subjective methods of study[22-28] uniformly indicated good results but this is true of most evaluations of therapy in angina pectoris, where purely subjective criteria are employed. Several objective studies showed improvement in the exercise electrocardiogram or clinical

exercise tolerance in a high percentage of patients.[10, 29-33] In other instances[6, 34-36] similar objective studies gave less favorable results. Winsor and Scott[33] found the drug to be effective when administered sublingually.

Triethanolamine trinitrate biphosphate, like nitroglycerin, has 3 -ONO_2 groups; the structural configuration, however, resembles pentaerythritol tetranitrate rather than nitroglycerin.

This nitrite was introduced following favorable reports from Europe.[37-39] Experiments on the isolated rabbit heart demonstrated coronary vasodilatation.[40] Several clinical evaluations reported favorable subjective results.[41-43] However, poor results have been reported by one group of workers, who also evaluated the drug by clinical observation,[44] and by another group,[10] who evaluated the drug by electrocardiographic measurements after exercise and compared the results with those following other preparations including pentaerythritol tetranitrate and Nitroglyn.

Sodium nitrite is the simplest nitrite available. Studies in laboratory animals[45] indicated that it is a highly effective coronary vasodilator but it has proved ineffective when given in 60 mg. doses to patients with angina pectoris.[1] In laboratory studies the drug is given parenterally and in doses (considering the weight of the subjects) considerably larger than those given orally to human subjects.

Methods

The methods of study have been described in detail elsewhere.[4, 6, 46] In brief, they involved the following steps:

Subjects

A group of typical patients with angina pectoris were observed for many weeks, both without treatment and while taking placebos, in order to evaluate the severity and relative constancy of symptoms.

The 34 subjects of the present study included 20 men and 14 women. All but 2 patients were 51 years of age or older. In each instance the angina pectoris was due to coronary artery disease. These 34 patients were similar to other groups previously studied in this laboratory except for a higher percentage of women and a higher percentage of patients who responded favorably to nitroglycerin.

Methods of Observation. At weekly intervals, for many months, the clinical response to therapy was evaluated by 2 physicians while another physician independently measured the amount of exercise necessary to induce angina under standardized conditions. The standardized conditions of the exercise tolerance test are important.[4, 46, 47] They involve repeated trips over a 2-step staircase in a relatively cold environment (45 to 55 F.) until an attack of angina, typical for that patient, is precipitated.

Medication. The 6 nitrites were administered in at least 21 different shapes, colors, vehicles, or concentrations. Placebos in at least 10 different forms were also administered.

The first medication prescribed was invariably a placebo. Thereafter, there was no uniform order except that each beneficial response was followed by a placebo and later by re-administration of the apparently effective medication in disguised form. As a result of these precautions, neither the patient nor the observer who measured the standardized exercise tolerance could recognize the medication. Thus, the conditions of the "double-blind test" were fulfilled.

Routes of Administration, Dosage and Time of Measurements

The 6 nitrites were given sublingually (or bucally), subcutaneously (or intramuscularly), by mouth (to be swallowed), and by inunction. The doses employed were those recommended by the manufacturer as adequate and several times larger if the recommended dose proved inadequate. Except when given parenterally, the medication was taken several times daily for at least 1 week before the response was measured. The Standardized Exercise Tolerance was measured at a time appropriate for demonstrating the effect of the morning dose.

Sublingual or Buccal Therapy. Medication was taken 3 times daily after meals. The Standardized Exercise Tolerance Test was performed 2 minutes after an 0.3 mg. "hypodermic tablet" of nitroglycerin had dissolved under the patient's tongue; in most instances from 20 to 30 seconds were required for complete solution of the tablet.

Since the only available preparations of the other 5 nitrites were meant to be swallowed, these tablets were used for the sublingual or bucal pouch studies also. The exercise tolerance was measured within 20 minutes after these tablets had dissolved except when the duration of action was studied.

The erythrol tetranitrate was obtained from 3 sources. The tablets contained 15 mg. of erythrol tetranitrate when prepared. Some deterioration must have taken place because freshly opened bottles gave off a distinct odor of nitric acid and the cotton wadding in 1 preparation had disinte-

grated to powder. Two of the preparations (those marketed by Burroughs Wellcome Co. and Merck and Co.) usually required from 1 to 1½ hours in contact with the oral mucosa for disintegration; the latter product is no longer available commercially. The third preparation (a Merck product, marketed by Sharpe and Dohme Co.) disintegrated more rapidly, usually in ½ to 1 hour, and contained 15 mg. of active drug in a 230-mg. tablet.

The mannitol hexanitrate contained 32.5 mg. of the drug in a tablet weighing 494 mg. These tablets were quite large. They dissolved or disintegrated sublingually in about 15 minutes. The dose used was 65 mg. 3 times daily.

Two preparations, each containing 2 mg. of triethanolamine trinitrate biphosphate (Metamine) were used in doses of 1 to 4 tablets 3 times daily.

Pentaerythritol tetranitrate (Peritrate) was obtained from 2 sources* as tablets of 10 or 20 mg. The doses were usually 40 to 50 mg. 3 times a day; several subjects also received 10 mg., 3 times a day. The exercise tolerance tests were performed within ½ hour after sublingual solution of the tablets.

In most instances, the dose of sodium nitrite was 0.3 Gm. (5 tablets). Patients who experienced faintness with this dose were given smaller doses but usually had similar untoward reactions with as little as 60 mg.

Parenteral Administration. The Standardized Exercise Tolerance Test was performed 20 minutes to ½ hour after a single injection of medication. During the preceding week these patients had taken placebos by mouth, 3 times daily.

Nitroglycerin was given subcutaneously in doses of 0.3 mg.

Erythrol tetranitrate used for subcutaneous administration was obtained by extraction of the active principle from the tablets with alcohol and ether. This extract was then mixed with lactose, made into hypodermic tablets, and assayed for potency. Erythrol tetranitrate is only slightly soluble in water, so that much of the 15 mg. dose was probably in suspension when injected hypodermically.

The solution of triethanolamine trinitrate biphosphate for parenteral administration was supplied by the manufacturer. The dose employed was 4 mg., administered intramuscularly. Unfortunately, its use was followed by considerable, although temporary, local pain, which may have decreased its efficacy.

Sodium nitrite was administered intramuscularly in doses of 0.06 to 0.18 Gm.

Mannitol hexanitrate and pentaerythritol tetranitrate were not given parenterally.

*Maltbie Laboratories and Warner Chilcott Co.

Oral or Swallowed Medication. Nitroglyn was given twice daily, all others 3 times daily (on arising, at 2:00 to 3:00 p.m., and on retiring) for 1 week and the Standardized Exercise Tolerance Test was performed from 1 to 2 hours after the last morning dose.

Nitroglycerin was given in 2 forms. In order to prevent absorption from the oral mucous membranes, hypodermic nitroglycerin tablets were encased in gelatin capsules before being swallowed. The minimum dose used in these studies was 0.45 mg. t.i.d. In order to determine the effective dose of nitroglycerin when swallowed, doses of 1 to 15 mg. (in capsules containing 1 mg. or 3 mg. each) were given to 13 patients. Studies with Nitroglyn were also carried out with varying doses.

Erythrol tetranitrate was administered in doses of 30 mg. 3 times daily for at least 1 week.

Mannitol hexanitrate was given in doses of 65 mg.

After preliminary studies with 2 mg. tablets, the dosage of triethanolamine trinitrate biphosphate used was 6 mg., 3 times daily for at least a week.

The dosage of pentaerythritol tetranitrate used was 40 to 50 mg. 3 times a day; several subjects also took 10 mg. 3 times a day.

Twenty-nine patients were requested to take 300 mg. of sodium nitrite 3 times daily for 1 week. Patients who developed untoward effects to this dose were given smaller doses.

Inunction. These studies were carried out with nitroglycerin and erythrol tetranitrate ointments.

Four inches of Nitrol Ointment (containing approximately 43 mg. of nitroglycerin) were rubbed in well twice daily for 1 week. The Standardized Exercise Tolerance Test was performed approximately 2 hours after the last dose.

The erythrol tetranitrate material for inunction was made by incorporating the specially prepared hypodermic tablets in a water soluble ointment base. An amount containing approximately 65 mg. of erythrol tetranitrate was rubbed in well, morning and night for 1 week and the exercise test carried out 2 hours after the last application.

Analysis of Results

The results were evaluated by studying the patient's record of the number of attacks experienced during each period of therapy; by asking the patient's opinion of the effectiveness of the treatment; and, most important, by measurement of the patient's exercise tolerance under the standardized conditions of the test. The following degrees of response were recognized.

Marked response. The patient was able to perform at least 25 per cent more work without angina than when taking placebos and stopped exercise because of dyspnea or fatigue, rather

than pain; or angina was induced but only after a 50 per cent increase in exercise above the level with placebos.

Moderate Response. Angina did not occur but the increased work was no more than 24 per cent; or angina was induced after an improvement of exercise tolerance of 20 to 49 per cent.

Slight response. This implied a 10 to 19 per cent increase in exercise tolerance before angina was precipitated.

No response. Angina was induced after no more exercise than the maximum that could be performed during the placebo period. A decrease in exercise tolerance was not infrequent in these cases. In such instances the medication failed to improve the patient's condition sufficiently to overcome the deleterious effects of factors that increase the tendency to attacks (emotion, intercurrent illness, etc.). This apparent decrease in exercise tolerance does not imply that the clinical condition was made worse; it must be remembered that the change in exercise tolerance was determined by comparison with the *maximum* amount of work that the patient could perform while taking placebos.

All positive and many negative results were checked by re-administering the drug at a later date in disguised form or by comparison with the response to larger doses, except in a few instances where a change in the patient's condition (complete remission of symptoms, progression of disease, unavailability of the patient, etc.) prevented repetition.

As in previous studies[2, 4, 6, 47-50] the patients were divided into 3 groups according to the increase in their exercise tolerance 2 minutes after the solution sublingually of 0.3 mg. nitroglycerin.

Group 1 included those patients who had a "marked response" to sublingual nitroglycerin.

Group 2 patients had a "moderate response" to sublingual nitroglycerin.

Group 3 patients showed "slight response" or "no response" to sublingual nitroglycerin.

Electrocardiographic Studies.

These were carried out in a few patients to demonstrate coronary vasodilator activity according to methods previously described.[4, 6, 48, 51] Coronary vasodilatation was indicated by prevention of S-T depression in lead 4R after the same amount of work that caused definite S-T depression plus an attack of angina pectoris when the patient was taking placebos.

Results

The results are presented in tables 1 and 2. As in previous studies[2-6, 47, 50, 52] the 20 group 1 subjects were far more likely to respond to other medication than were the 5 group 2 or the 9 group 3 patients. Comparison of the effects of medication, therefore, is best observed in group 1 subjects (fig. 2).

Nitroglycerin

Sublingual Administration. The dosage used caused no untoward effects in the 34 subjects. Thirteen of the 20 group 1 patients were able to exercise until fatigued without developing angina. The remaining 7 were able to increase their exercise tolerance by 62 to 135 per cent before they developed angina.

Subcutaneous Administration. In 7 of the 10 group 1 subjects, the degree of beneficial response was comparable to that following sublingual administration of the same dose.

Oral Administration. Thirteen of the 15 group 1 subjects who swallowed capsules containing 0.45 mg. of nitroglycerin showed no significant response while only 2 showed "moderate" increases in exercise tolerance.

The swallowed dose of nitroglycerin necessary to increase the ability to exercise is shown in table 3. In 11 group 1 subjects, a "marked response" required a minimum of 2 or 3 mg. in 3 patients, 5 or 6 mg. in 2 patients, and 15 mg. in 2 patients. Two other patients showed a moderate response to 2 or 4 mg. but did not receive larger doses. The remaining 2 subjects failed to show a response after 15 mg. There were no untoward effects.

Fourteen group 1 subjects received Nitroglyn (table 3). Six showed a "marked response;" 1, after 1 tablet (6 mg.); 2, following 12 mg.; 3 required 18, 24, and 30 mg., respectively. Two additional patients showed a "moderate response" after 12 and 24 mg., respectively. Two patients showed no response to as much as 30 mg. The remaining 4 showed no response after 12 mg., but received no larger doses.

Administration by Inunction (table 4). One of 6 group 1 patients showed a "marked response" to Nitrol Ointment and 3 others showed responses that were "moderate" but appreciably less than followed sublingual nitroglycerin in the same patients.

TABLE 1.—*Comparative Efficacy of Six Nitrites Administered Sublingually, Subcutaneously, and by Swallowing*

Patient	Sex	Age	Usual S.E.T.T. trips Placebos	INCREASE IN STANDARDIZED EXERCISE TOLERANCE (per cent)																	
				Nitroglycerin			Erythrol tetranitrate			Mannitol hexanitrate			Triethanolamine trinitrate biphosphate			Pentaerythritol tetranitrate			Sodium nitrite		
			S.L. and P.O.	S.L.	S.Q.	P.O.	S.L.	S.Q.	P.O.	S.L.	P.O.		S.L.	S.Q.	P.O.	S.L.	P.O.		S.L.	S.Q.	P.O.
Group 1																					
H.N.	M	67	24–28	142†	78†	14	36†	43	36	75†	25		50		0	36	43		21	36	21
I.K.	M	63	16–23	135	74†	13	74	35	39	—	—		X	- 4	-13	22	- 4		-17	48	39
M.Ke.	F	60	25–30	120†	13	27	47	-17	47	—	—		20	-17	-23	7	-27		-13	X	X
M.R.	M	51	29–34	106†	—	15	41†	—	53	65	47		X		0	44	29		X	—	12
E.W.	F	65	19–23	93	—	13	43	—	13	30	- 9		22	—	9	43	35		—	—	- 4
M.Ko.	M	53	36–44	89	—	-16	0†	—	-52	—	—		-23	—	-39	-20	- 5		-36	—	-18
S.C.	F	63	22–26	81†	—	—	31	—	16	—	—		—	—	—	—	-16		X	—	X
F.D.	F	50	26–30	76	—	- 3	33	—	-33	—	—		—	—	—	—	—		X	—	- 7
G.B.	M	72	28–35	74	—	—	57	—	31	—	—		—	—	—	—	—		26	—	—
R.Sh.	F	41	45–60	67†	67†	-31	13	—	-47	—	—		X	—	-27	22	-47		—	—	X
M.B.	M	74	29–33	67†	67†	- 6	100†*	21	-12	—	—		39*	21	-33	15	- 9		21	82†	- 9
P.M.	F	64	6–14	64	—	—	50†	—	0	—	—		—	—	—	0†	-36		X	—	-21
R.L.	F	63	20–26	62	19	0	- 4	-15	-31	23	15		-15	—	-38	- 7	-38		- 7*	—	- 7*
T.K.	M	51	68–75	60†	—	13	33†*	—	84†*	33†	-17		—	—	9	40†	31		-17	—	- 9
A.T.	F	64	18–27	48†	-33	-33	74†	44†	- 4	—	—		89	0	-33	-15	-15		-19	-30	30
M.F.	F	59	54–76	45†	32†	-30	5†	—	- 1	—	—		0	—	-32	32†	32†		7†	—	-28
A.C.	M	68	26–36	44†	—	—	0†	—	- 6	—	—		—	—	—	—	—		—	—	—
H.S.	M	53	65–70	42†	—	—	29	—	7	7	- 3		—	—	—	11	—		—	—	43†
M.P.	M	58	30–37	35†	-16	-22	13	—	-27	—	—		3	11	-35	0	5		11	13	- 8
P.S.	M	48	23–28	25†	43	36	50†	32	43†	—	—		—	—	—	—	-43		14	—	25†
Group 2																					
M.C.	M	56	20–24	42	—	50	33	—	63	—	—		—	—	—	—	67		—	—	- 4
E.R.	F	72	20–27	41	11	4	- 4	-19	-11	—	—		-48	-26	-11	—	-11		—	—	-33
E.S.	F	59	24–32	31	—	-19	- 6	—	-19	—	—		—	—	-31	—	-19		-37	—	—
J.M.	M	54	36–43	16†	—	2	12	53†	- 7	—	—		-12	—	- 2	—	—		—	—	—
J.K.	M	50	40–48	13†	—	—	-17	—	15†	—	—		—	—	—	—	13		—	—	—
Group 3																					
J.S.	M	61	14–29	17	-34	-59	-21	- 7	-41	—	—		—	—	—	—	-52		—	—	-38
T.Mc.	M	65	33–36	6	3	- 6	- 6	-11	8	-17	- 6		- 6*	-11	-11	-17	-17		- 6	-11	- 6
A.Z.	M	58	20–24	0	8	0	8	33	-17	—	—		25	25	8	25	- 8		8	17	0
M.Ko.	F	60	16–20	0	-10	-10	0	-15	-25	—	—		—	—	—	—	- 5		-10	- 5	0
F.B.	F	54	30–34	-12	-12	- 6	0	-15	-18	—	—		-20	-12	-23	-29	-18		-26	0	-32
M.D.	F	46	30–38	-24	—	-27	-16	—	—	—	—		—	—	—	—	—		—	—	—
M.G.	M	49	17–25	-28	-44	-28	0	—	-24	—	—		-28	—	-28	-20	-52		—	—	-68
R.Sm.	F	56	18–20	-30	-15	- 5	-35	—	X	—	—		0	-15	-10	15	25		—	—	—
H.C.	M	59	16–22	-36	—	—	-14	—	-36	—	—		—	—	—	14	5		-18	—	—

S.E.T.T., Standardized Exercise Tolerance Test; S.L. Medication administered sub-lingually or in buccal pouch; S.Q., Medication administered subcutaneously or intramuscularly; P.O. Medication administered by mouth.
† No attack of angina pectoris induced.

– A Decrease in exercise tolerance as compared with the maximum amount that could be performed during the placebo trial.
* Medication followed by untoward effect.
X Medication stopped because of untoward effect.

TABLE 2.—*Summary—Comparative Efficacy of Six Nitrites Administered Sublingually, Parenterally, and by Swallowing*

		Nitroglycerin			Erythrol tetranitrate			Mannitol hexanitrate		Triethanolamine trinitrate biphosphate			Penta-erythritol tetranitrate		Sodium nitrite		
		S.L.	S.Q.	P.O.	S.L.	S.Q.	P.O.	S.L.	P.O.	S.L.	S.Q.	P.O.	S.L.	P.O.	S.L.	S.Q.	P.O.
Group 1	Number of subjects	20	10	15	20	7	20	6	6	12	5	13	15	17	16	6	18
	Untoward effects	0	1	0	2	0	1	0	0	4	0	0	0	0	5	1	4
	Marked response	20	6	0	9	1	2	3	0	2	0	0	2	1	0	1	2
	Moderate response	0	1	2	8	4	5	2	2	3	1	0	6	4	4	2	3
	Slight response	0	2	5	2	0	2	0	1	0	1	0	2	0	2	1	1
	No response	0	1	8	1	2	11	1	3	4	3	13	5	12	6	1	9
Group 2	Number of subjects	5	1	4	5	2	5	0	0	2	1	3	0	4	1	0	2
	Untoward effects	0	0	0	0	0	0	—	—	0	0	0	0	0	0	0	0
	Marked response	0	0	1	0	1	1	—	—	0	0	0	0	1	0	0	0
	Moderate response	5	0	0	1	0	1	—	—	0	0	0	0	0	0	0	0
	Slight response	0	1	0	1	0	0	—	—	0	0	0	0	1	0	0	0
	No response	0	0	3	3	1	3	—	—	2	1	3	0	2	1	0	2
Group 3	Number of subjects	9	7	8	9	5	8	1	1	5	4	5	6	8	5	4	6
	Untoward effects	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
	Marked response	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Moderate response	0	0	0	0	1	0	0	0	1	1	0	1	1	0	0	0
	Slight response	1	0	0	0	0	0	0	0	0	0	0	2	0	0	1	0
	No response	8	7	8	9	4	7	1	1	4	3	5	3	7	5	3	6
Total	Number of subjects	34	18	27	34	14	33	7	7	19	10	21	21	29	22	10	26
	Untoward effects	0	0	0	2	0	2	0	0	5	0	0	0	0	5	1	4
	Marked response	20	6	1	9	2	3	3	0	2	0	0	2	2	0	1	2
	Moderate response	5	1	2	9	5	6	2	2	4	2	0	7	5	4	2	5
	Slight response	1	3	5	3	0	2	0	1	0	1	0	4	1	2	2	1
	No response	8	8	19	13	7	21	2	4	10	7	21	8	21	12	4	17

S.L., Medication administered sublingually or in the buccal pouch; S.Q., Medication administered subcutaneously or intramuscularly; P.O., Medication administered by mouth.

Erythrol Tetranitrate

Sublingual or Buccal Administration. In the 20 group 1 patients the magnitude of the response to 15 mg. was comparable to that following nitroglycerin in 9 subjects, somewhat less, but of considerable benefit in 8, and of little value in the remaining 3 patients. In accordance with previous studies, the clinical response during the weeks of administration was uniformly excellent in those patients who showed a "marked" or a "moderate response."

Patients did not object to sublingual or buccal use of the drug during the comparatively short period of study. Severe pounding headache similar to that experienced by some patients after nitrogylcerin was reported by 2 of the total 34 patients. This was relieved by aspirin. More severe headache, sufficient to cause the patient to discontinue the medication, was reported by 4 patients who took 2 tablets (30 mg.).

The beneficial action of the drug did not become evident until 6 to 10 minutes after the drug was placed under the tongue. The duration of action persisted for at least 1 to 2 hours after dissolution of the tablet (table 5).

Subcutaneous Administration. Five out of 7 group 1 patients responded to parenteral injection but the increase in exercise tolerance was somewhat less than what followed sublingual administration.

Oral Administration. Swallowing 30 mg. of erythrol tetranitrate was distinctly less beneficial than sublingual or subcutaneous administration of 15 mg. (table 2).

Administration by Inunction. The results were similar to those obtained with nitroglycerin ointment in 6 of the 7 patients studied (table 4).

Mannitol Hexanitrate

Here again the nitrite was comparatively ineffective when swallowed but highly effective when given by the sublingual route. There were no untoward effects.

Triethanolamine Trinitrate Biphosphate

Sublingual Administration. Of 12 group 1 subjects, 2 showed a "marked response," 3 a "moderate response," 4 "no response," and 3 discontinued the therapy because of painful sublingual stomatitis. One additional patient (who showed a "moderate response") had a similar stomatitis but continued therapy. In general, the increase in exercise tolerance was less than after sublingual erythrol tetranitrate or nitroglycerin.

Oral Administration. All 21 patients who swallowed 6 mg. of Metamine 3 times a day for at least 1 week showed "no response." There were no headaches or other untoward effects.

Parenteral Administration. One out of 5 group 1 patients had a "moderate response."

Pentaerythritol Tetranitrate

This drug was not administered parenterally or by inunction.

Sublingual Administration. Two out of 15 group 1 subjects showed a "marked response," and 6 a "moderate response." There were no untoward reactions. In general the magnitude of the response was less than that following nitroglycerin, but somewhat greater than when pentaerythritol tetranitrate was swallowed.

Oral Administration. Out of 17 group 1 patients 1 showed a "marked response," and 4 a "moderate response." There were no untoward reactions.

Sodium Nitrite

The route of administration did not affect the results as strikingly as with other preparations used in this study, but untoward effects were frequent and related to peripheral rather than intracranial dilatation.

Sublingual Administration. This was employed in 16 group 1 patients. No patient had a "marked response," while 4 had a "moderate response." Four patients omitted the drug because of faintness; 1 additional patient continued the drug despite faintness and showed no therapeutic response.

Subcutaneous Administration. One of the 6 group 1 subjects had a "marked response," 2

TABLE 3.—*Comparative Effectiveness of Nitroglycerin Given Sublingually and Orally*

	Patient	Sex	Age	Placebos	NITROGLYCERIN—increase in exercise tolerance—(per cent)										
					"Hypo." tablets	Capsules given orally (dose in mg.)						Nitroglyn given orally (dose in mg.)				
				Usual S.E.T.T. trips	S.L.											
					0.3 mg.	0.45	1.–2.	3.–.4	5.–6.	8.	15.	6.	12.	18.	24.	30.
Group 1	H.N.	M	67	24–28	142†	14	64	86	157	86	84	22	36†	93	71†	108†
	I.K.	M	63	16–23	135	13	0	–13	– 9	0	4	—	39	—	—	—
	M.Ke.	F	60	25–30	120†	27	20	—	—	—	—	—	–20	—	—	—
	M.R.	M	51	29–34	106†	15	6	38	85	85	118	23	73	50	76	118
	E.W.	F	65	19–23	93	13	13	26	48	48	48	13	26	13	22	52
	M.Ko.	M	53	36–44	89	—	—	—	—	—	—	—	—	45*	—	—
	S.C.	F	63	22–26	81†	—	—	—	—	—	—	– 4	8	23	0	15
	F.D.	F	50	26–30	76	– 3	—	—	—	–23	3	–47	10	—	13	3
	R.Sh.	F	41	45–60	67†	–31	28	67†	45†	—	—	70†	—	—	—	—
	M.B.	M	74	29–33	67†	—	—	—	—	—	—	9	– 3	—	—	—
	R.L.	F	63	20–26	62	–31	—	23	16	16	54	8	34	61	61	—
	T.K.	M	51	68–75	60†	—	13	1	—	19	47†	—	—	—	—	—
	A.T.	F	64	18–27	48†	—	—	—	—	—	—	–41	–26	—	—	—
	M.F.	M	69	54–76	45†	–30	32†	26	37†	—	—	—	—	—	—	—
	A.C.	M	68	26–36	44†	—	–50	0†	—	—	—	—	—	—	—	—
	H.S.	M	53	65–70	42†	—	—	—	—	—	—	—	20	19	43†	—
	M.D.	M	58	30–37	35†	—	—	—	—	—	—	—	0	—	—	—
Group 3	T.Mc.	M	65	33–36	6	– 6	– 6	–22	—	–22	–11	–11	– 6	—	–17	–22
	A.Z.	M	58	20–24	0	—	—	—	—	—	—	—	33	—	—	—
	F.B.	F	54	30–34	–12	–12	—	–18	—	—	– 3	–12	–23	–12	– 6	– 6

S.E.T.T., Standard Exercise Tolerance Test. S.L., Medication administered sublingually.

* Medication followed by headache.

† No attack of angina pectoris induced.

– A decrease in exercise tolerance compared with the maximum amount that could be performed during the placebo trial.

TABLE 4.—*Comparative Effect of Nitrites Given Sublingually and by Inunction*

	Patient	Sex	Age	Placebos (orally) S.E.T.T. trips	Increase in exercise tolerance (per cent)		
					Nitroglycerin S.L.	Ointment	
						Nitroglycerin	Erythrol tetranitrate
Group 1	H.N.	M	67	24–28	142†	71	50†
	I.K.	M	63	16–23	135	– 4	– 7
	M.R.	M	51	29–34	106†	47	0
	E.W.	F	65	19–23	93	26	18
	F.D.	F	50	26–30	76	–13	—
	M.F.	M	69	54–76	45†	29	24
Group 3	T.Mc.	M	65	33–36	6	–17	–17
	F.B.	F	54	30–34	–12	–18	–21

S.E.T.T., Standardized Exercise Tolerance Test; S.L., Medication administered sublingually.
†No attack of angina pectoris induced.
– A decrease in exercise tolerance as compared with the maximum amount that could be performed during the placebo trial.

TABLE 5.—*Speed of Onset and Duration of Action of Erythrol Tetranitrate Administered Sublingually to Group 1 Subjects*

Patient	Sex	Age	S.E.T.T. while taking placebos trips	Increase in S. E. T. after sublingual administration of erythrol tetranitrate (per cent)										
				Minutes after sublingual administration (before dissolved)					Hours after solution of tablet					
				3	6	10	15	20	Immediately	¼	¾	1	2	3	4
H.N.	M	67	24 – 28	—	—	—	—	—	36†	52†	50†	—	50†	50	46
I.K.	M	63	16 – 23	—	—	—	—	—	74	—	—	106	39	30	13
M.Ke.	F	60	25 – 30	—	—	—	—	—	47	—	—	–57	—	—	—
M.R.	M	51	29 – 34	12	50	24	184	146	41†	—	—	40	—	36	26
E.W.	F	65	19 – 35	40	82	57	78†	—	78†	44	13	13	—	—	—
M.B.	M	74	29 – 33	15	3	70	—	—	100†	70†	—	94†	88†	39	9
A.T.	F	64	18 – 27	—	—	—	—	—	74†	—	—	74	—	93	–18

S.E.T., Standard Exercise Tolerance; S.E.T.T., Standardized Exercise Tolerance Test.
† No attack of angina pectoris induced.
– A decrease in exercise tolerance compared with the maximum amount that could be performed during ing the placebo trial.

showed "moderate response," and 1 was not exercised because of faintness. Five subjects who had untoward reactions when given the drug by other routes did not receive it parenterally.

Oral Administration. Of 18 group 1 subjects who swallowed this drug 2 showed a "marked response," and 3 a "moderate response." Three discontinued the drug because of faintness, pallor, and sweating. Doses of 180 mg. and 60 mg. caused similar but less severe reactions, accompanied by a fall in blood pressure in these 3 patients, even when the 60-mg. tablet was disguised. One additional patient noted faintness but continued the drug.

Electrocardiographic Studies

Electrocardiographic studies before and after exercise were carried out in 8 subjects (4 in group 1, 1 in group 2, 3 in group 3), following the administration of placebos, nitroglycerin sublingually, and both erythrol

TABLE 6.—*Effect of Medication on the Degree of S-T Depression Induced by Exercise*

Subject	Placebo S.L. or P.O.		Nitroglycerin S.L.		Erythrol tetranitrate S.L.		Erythrol tetranitrate P.O.		Triethanolamine trinitrate biphosphate S.L.		Triethanolamine trinitrate biphosphate P.O.	
	Number of trips	S-T depression* (mm.)	Number of trips	S-T depression* (mm.)	Number of trips	S-T depression* (mm.)	Number of trips	S-T depression* (mm.)	Number of trips	S-T depression* (mm.)	Number of trips	S-T depression* (mm.)
Group 1												
H.N.	28	0.8	28†	0.0	—	—	28†	1.15	—	—	28	0.82
M.B.	33	0.95	33†	0.15	—	—	—	—	—	—	—	—
A.T.	27	2.5	27†	1.45	27†	1.8	27	1.25	—	—	—	—
M.P.	32	0.85	32†	0.0	30†	0.12	32	0.0	30†	0.67	30	−1.0
Group 2												
E.R.	20	1.6	20†	0.45	20	0.5	20	1.85	20	1.5	—	—
Group 3												
T.Mc.	30	6.4	30†	3.25	30†	2.72	28	4.0	32	2.25	30	2.85
A.Z.	22	0.95	22	0.15	—	—	—	—	—	—	—	—
F.B.	30	0.95	30†	1.0	—	—	—	—	25	0.7	25	0.55

S.L., Medication administered sublingually or in buccal pouch; P.O., Medication administered by mouth.
* Average of 10 consecutive complexes.
† No attack of angina pectoris induced.

tetranitrate and triethanolamine trinitrate biphosphate administered sublingually and by swallowing (table 6).

The S-T depression in lead 4R after exercise was appreciably less in 6 out of 7 subjects who received nitroglycerin sublingually, in all 4 subjects who received erythrol tetranitrate sublingually, in 3 out of 5 who received this drug by mouth, in 2 out of 4 who received Metamine sublingually, and in 2 out of 4 who took this drug by mouth.

DISCUSSION

In this study, as in previous studies,[2,5,6,48-50] a "marked response" or a "moderate response" to medication as measured by the Standardized Exercise Tolerance Test, was of clinical significance. Patients who showed this degree of response experienced no attacks or almost no attacks in daily life while taking the medication, and such results were reproduced even when the medication was disguised. In contrast, a "slight response" to medication was of no clinical significance and any apparent clinical improvement was fortuitous or due to the patient's faith in therapy and was not likely to be persistent or reproducible. Since group 1 subjects (those who show a "marked response" to nitroglycerin administered sublingually) are the ones most likely to respond to other effective medication, study of this group makes it possible to compare the effectiveness of medication with a minimum of confusing data (fig. 2).

Not only do patients differ greatly in their response to treatment, but drugs also differ considerably in their effectiveness in preventing attacks of angina pectoris. In accord with previous studies[2, 3, 5, 6] therapeutic measures can be divided into 3 groups. Group A includes drugs that are highly effective both clinically and by exercise tolerance studies in a large number of patients, especially group 1 subjects (those responding to sublingual nitroglycerin). Group B includes drugs of only moderate value in such subjects. Group C drugs are of little or no value.

Nitroglycerin. When administered sublingually, nitroglycerin is the most effective of all group A drugs in common use. Not only do more patients show a response to this form of treatment, but the degree of response (i.e., the amount by which the patients' exercise tolerance can be increased before angina is induced) is greater than is observed after any other medication. Because of its short dura-

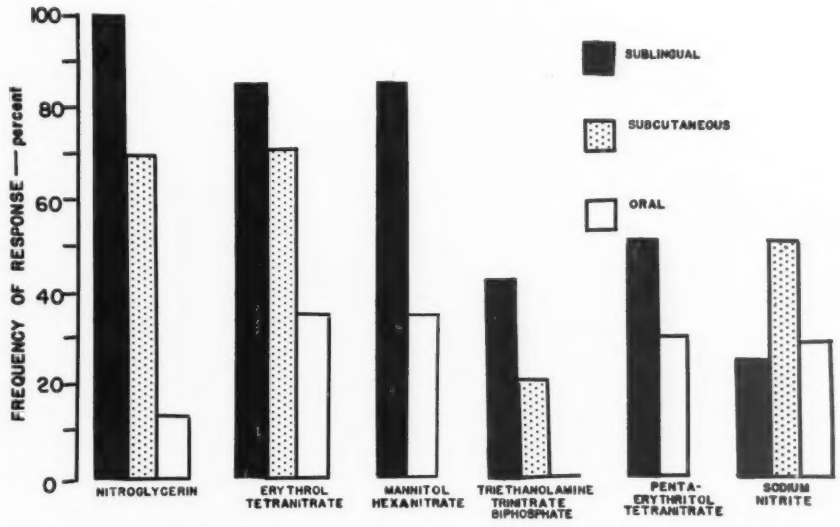

FIG. 2. Frequency of moderate or marked response of group 1 subjects to 6 nitrites administered sublingually, subcutaneously, and when swallowed.

tion of action, the prophylactic use of this drug is usually limited to administration immediately before undertaking any task.

Nitroglycerin administered by mouth, on the other hand, is a group C drug and is of little clinical value to most patients in the doses usually employed. To be effective when swallowed, a single dose of nitroglycerin must be many times larger than the usual sublingual one (table 3). The reasons for this marked difference in effectiveness is not known. The equal effectiveness of nitroglycerin given subcutaneously and sublingually suggests that the drug is inactivated in the gastrointestinal tract. Hypodermic administration of nitroglycerin has limited value in clinical practice because of the inconvenience of self-medication; it might be of value in the treatment of acute exacerbations of the disease, but sublingual administration is as effective and simpler to use.

The results with Nitroglyn, a pharmaceutical preparation of nitroglycerin intended for oral use, are in accord with these findings. Nitroglyn is a group B drug. It was of marked or moderate value in 57 per cent of 14 group 1 patients, but only in doses that were 2 to 4 times larger than that advocated by the manufacturer and many times larger than originally advised. At least part of the lack of objective evidence of the usefulness of nitroglycerin when given by mouth may be due to the short duration of action, if so, it limits further the clinical value of this form of treatment.

The effectiveness of nitroglycerin by inunction (group B) is of interest because it illustrates the well-known fact that this drug can be absorbed through the unbroken skin. This characteristic is responsible for the headaches of workers manufacturing dynamite. The lack of popularity of treatment by inunction further limits its value in present day clinical therapy of angina pectoris.

Erythrol Tetranitrate. According to the present and previous studies in this laboratory[1, 2] erythrol tetranitrate, when swallowed, is a group B therapeutic agent, i.e., it is effective to a moderate degree in a small percentage of patients. In marked contrast, however, are the results of the present investigation that erythrol tetranitrate, given sublingually, is one of the most highly effective group A agents. The frequency of this beneficial action and the degree of increase in exercise tolerance

after sublingual erythrol tetranitrate approximate the effects of nitroglycerin, amyl nitrite, and octyl nitrite more closely than do any other of the approximately 100 preparations tested in this laboratory. Furthermore, the duration of this beneficial action is prolonged sufficiently to make this method of treatment of practical clinical value. On the other hand, the speed of onset of action is too slow to permit its use for the treatment of individual attacks. Further studies of the speed of onset and duration of action are advisable with tablets especially prepared for sublingual or buccal use, but the solubility of erythrol tetranitrate in water is much less than that of nitroglycerin and it is unlikely that it can replace the latter drug for the treatment of individual attacks. The slow disintegration time of the available tablets may be of some added value in prolonging the duration of action. The absence of local discomfort makes it possible to retain the tablet in the buccal pouch for prolonged periods without interfering with normal activity (including speech); for obvious convenience, it is probably advisable to use the drug after meals.

With the doses used (15 mg. t.i.d.) headache was infrequent; with larger doses (30 mg.) severe pulsating headache was often troublesome. This is probably due to intracranial vasodilatation and is additional evidence of the drug's activity; it is seen frequently with large doses of the active nitrites such as nitroglycerin, amyl nitrite, and octyl nitrite[5, 53-55] as well as with erythrol tetranitrate, but it is not seen with the other weaker nitrites used in this study, nor with other weak vasodilators such as the purines and the cinchona alkaloids.[1, 6, 52]

The beneficial results of erythrol tetranitrate when given subcutaneously or by inunction are additional evidence of its absorption parenterally and from the skin respectively. This action is probably of limited clinical application.

Mannitol Hexanitrate. It is evident from the present as well as previous exercise tolerance studies[2, 21] that this is a group B drug when swallowed in doses of 65 mg. 3 times daily. In contrast, although the number of subjects in the present series is small, it is evident that mannitol hexanitrate is a group A drug when administered sublingually.

The practical clinical value of this therapeutic procedure is decreased considerably by the size of the tablets available on the market. The commercially available tablets are large because the Bureau of Explosives has advised that mannitol hexanitrate be diluted with at least 10 parts of inert material to assure safety in transportation. This degree of dilution may not be essential, however, for although the American preparation of its close relative, erythrol tetranitrate (Merck) also is marketed in a dilution of 1:15, the British preparation (Burroughs Wellcome) has been marketed for years in approximately a 1:2 dilution.

It is evident that as the number of carbon atoms in the chain, or as the size of the molecule is increased, the vasodilator activity is decreased even though the number of $-ONO_2$ groups may be increased. Thus the effective sublingual dosages for nitroglycerin, erythrol tetranitrate, and mannitol hexanitrate is 0.3, 15, and 65 mg., respectively, while the effective sublingual doses for Peritrate and Metamine are considerably larger than that of nitroglycerin.

Triethanolamine Trinitrate Biphosphate (Metamine). Here again the drug was much more effective when given sublingually or by injection than when given by mouth. Headache was not experienced; this suggests that its vasodilating action is comparatively weak. Other untoward effects, however, (e.g., stomatitis when given sublingually and pain when given intramuscularly) limit its usefulness by these more effective routes.

Pentaerythritol Tetranitrate. This drug is of definite but moderate value in a small percentage of patients. It is classified, therefore, as a group B drug. There was no great difference in the frequency or degree of its effectiveness by the sublingual or by the oral route. This is in accordance with the fact that it is not readily absorbed from the skin or gastro-

intestinal tract;[12, 13] and also with the report that munitions workers who handle the chemical do not develop the typical nitrite headache.

The frequency of beneficial results with pentaerythritol tetranitrate in the subjects of the present series would seem to be less than that demonstrated by the objective electrocardiographic studies of Russek et al.[10, 31] This difference, however, is probably not as great as would appear, because Russek's subjects were limited to those whose electrocardiographic changes following exercise could be prevented by the administration of nitroglycerin. It would appear, therefore, that Russek's subjects corresponded to the more susceptible group 1 patients of the present series and such patients are likely to respond to pentaerythritol tetranitrate.

Sodium Nitrite. The discrepancy between the striking responses reported in animal experiments[45] where the drug was given parenterally and the comparative ineffectiveness of the drug when given orally to patients with angina pectoris[1] is probably due at least in part to the different routes of administration employed in these 2 studies and in part to the much smaller doses usually given clinically.

It is evident that larger doses (300 mg. t.i.d.) are much more effective than the 60 mg. doses usually employed in men. The drug is equally effective when absorbed from either the buccal mucosa or the gastrointestinal tract, but it is more effective when given parenterally. The frequency of effectiveness parenterally would probably have been greater in the present series if it had been administered to the 5 additional patients who developed untoward reactions when taking the drug sublingually or by mouth. The untoward reactions from this drug are quite different from, and more frequent than, those seen following the other nitrites. Headache was not encountered but hypotensive reactions occurred in over one third of the group 1 patients. This further limits the clinical usefulness of the drug in the treatment of angina pectoris.

Electrocardiographic Studies. Nitroglycerin, erythrol tetranitrate, and Metamine in the present series and with pentaerythritol tetranitrate in other series[10, 31] yield objective electrocardiographic evidence of a true pharmacodynamic activity indicating that they prevent or diminish myocardial anoxia, presumably by coronary vasodilatation. Such electrocardiographic studies cannot be accepted as evidence of therapeutic efficiency, however, for the following reasons: 1. There is no constant relationship between the occurrence of the electrocardiographic changes and the occurrence of cardiac pain. 2. Only a small percentage of angina patients are suitable for such studies.[4, 31, 51] Thus, although electrocardiographic studies after exercise or anoxemia demonstrate a pharmacologic effect, they yield no information concerning the frequency of beneficial clinical effect in the preponderant percentage of patients who are not suitable for such electrocardiographic studies. 3. Technical difficulties make it difficult to reproduce identical results on repeated tests. This is especially true in patients with angina pectoris because the electrocardiogram at rest may show varying degrees of S-T depression spontaneously on different days.

Untoward Effects. The occurrence of headache with nitrate therapy has been discussed. It is of short duration and can be avoided by decreasing the dose or can be treated with aspirin. The possibility of other untoward effects with prolonged use of the nitrites, although unlikely, must be kept in mind.

Early reports[56, 57] suggested the possibility of methemaglobinemia because of cyanosis or a brown discoloration of the blood. Early spectrophotometric methods, although more specific than these clinical observations, were subject to inaccuracies and inconsistencies.[58-62] Modern hemoglobin spectrophotometry,[63-65] which permits precise diagnosis, has shown methemaglobinemia in cases of sodium nitrite poisoning,[66, 67] but it has been pointed out that this is unlikely with therapeutic doses.[62]

Angina pectoris and even cardiac deaths have been encountered in young munitions

workers who manufacture dynamite from nitroglycerin. This may be due to reactive vasoconstriction that may occur when the drug is withdrawn abruptly after prolonged exposure to large doses. The necessity for industrial safeguards for munitions and pharmaceutical workers who have prolonged or frequent exposure to nitrites has been stressed.[61, 68] This type of withdrawal reaction has not been reported following therapeutic doses.

Hypotension, cardiovascular collapse, and myocardial infarction have been reported following nitroglycerin[69-71] or octyl nitrite,[5] especially in patients consuming significant amounts of alcohol while taking nitrites.[61, 72] Such reactions are readily avoided by adjusting the dosage and especially by avoiding overdosage such as may occur if the rapidly acting nitrites are administered repeatedly with only a few minutes between doses.

Summary

The comparative value of 6 different nitrites in the treatment of angina pectoris when administered by the oral, sublingual, subcutaneous, and percutaneous routes was studied in 34 patients by measuring the amount of work that could be performed under standardized conditions without inducing angina and also by observing the clinical response and the exercise electrocardiogram.

Glycerol trinitrate, erythrol tetranitrate, mannitol hexanitrate, and triethanolamine trinitrate biphosphate were all much more effective sublingually than when swallowed.

Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most effective of all prophylactic agents available for the treatment of patients with angina pectoris. The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use.

Nitroglycerin and erythrol tetranitrate were also effective when administered parenterally or by inunction but their value was markedly limited when swallowed. This suggests that these nitrites are inactivated in the gastrointestinal tract. Mannitol hexanitrate also was more effective sublingually than when swallowed but was of limited clinical value because of the large size of the tablets available. Triethanolamine trinitrate was moderately effective when administered sublingually but of no demonstrable value when swallowed. Sublingual therapy with this drug is limited because of the frequent glossitis that follows its use.

Pentaerythritol tetranitrate showed little difference in the frequency of response when administered sublingually or when swallowed, but the increase in exercise tolerance was somewhat greater following sublingual administration. This drug was only of moderate value in the treatment of patients with angina pectoris.

Sodium nitrite was more effective when given subcutaneously than when given sublingually or when swallowed, but the degree of value was low and the frequency of untoward reactions was too high to indicate clinical value.

Summario in Interlingua

Le valor comparative de 6 differente nitritos in le tractamento de angina de pectore, administrate per via oral, sublingual, subcutanee, e percutanee, esseva studiate in 34 patientes per mesurar le quantitate de labor que poteva esser executate sub conditiones standardisate sin induction de angina e etiam per observar le responsas clinic e le electrocardiogrammas a exercitio.

Glycerol trinitrate, erythrol tetranitrate, mannitol hexanitrate, e triethanolamino trinitrate biphosphate esseva omnes plus efficace in administration sublingual que post inglutition. Nitroglycerina e erythrol tetranitrato, quando administrate per via sublingual, es inter le plus efficace de omne le agentes prophylactic disponibile pro le tractamento de patientes con angina de pectore. Le comparativemente prolongate duration del action de erythrol tetranitrate post administration sublingual rende iste agente specialmente utile pro usos clinic.

Nitroglycerina e erythrol tetranitrate esseva etiam efficace quando administrate per via

parenteral o per inunction, sed lor valor esseva multo restringite post inglutition. Iste observation suggere que le duo nitritos es inactivate in le vias gastrointestinal. Etiam mannitol hexanitrate esseva plus efficace post uso sublingual que post inglutition, sed iste agente esseva de limitate valor clinic a causa del grande dimensiones del tablettas in que illo esseva disponibile. Triethanolamino trinitrate esseva moderatemente efficace quando administrate sublingualmente e sin valor demonstrabile quando inglutite. Le uso therapeutic de iste droga es restringite a causa del frequentia de glossitis que seque su administration sublingual.

Pentaerythritol tetranitrate differeva pauco in le frequentia del responsa post administration sublingual e post inglutition, sed le augmento del toleration de exercitio esseva levemente plus marcate post administrationes sublingual. Iste droga esseva solmente moderatemente utile in le tractamento de patientes con angina de pectore.

Nitrito de natrium esseva plus efficace quando administrate subcutaneemente que quando administrate sublingualmente o per inglutition, sed le grado de su valor esseva basse, e le incidentia de reactiones adverse esseva troppo frequente pro indicar un valor clinic.

REFERENCES

1. Riseman, J. E. F. and Brown, M. G.: Medicinal treatment of angina pectoris. Arch. Int. Med. **60**: 100, 1937.
2. —: The treatment of angina pectoris: A summary of ten years' objective study. New England J. Med. **229**: 670, 1943.
3. —: The present status of treatment in angina pectoris. Connecticut State M. J. **9**: 99, 1945.
4. Freedberg, A. S., Spiegl, E. D. and Riseman, J. E. F.: Objective evidence of the efficacy of medicinal therapy in angina pectoris. Am. Heart J. **22**: 494, 1941.
5. —, Riseman, J. E. F., and Spiegl, E. D.: Octyl nitrite in the treatment of angina pectoris. Am. Heart J. **22**: 519, 1941.
6. Riseman, J. E. F., Steinberg, L. A. and Altman, G. E.: Treatment of angina pectoris with cinchona alkaloids. Circulation **10**: 809, 1954.
7. Field, A. G.: On the toxical and medicinal properties of nitrate of oxyde of glyeyl. Med. Times & Gazette **16**: 291, 1858.
8. Murrell, W.: Nitro-glycerine as a remedy for angina pectoris. Lancet **1**: 80, 1879.
9. Evans, W. and Hoyle, C.: Prevention and treatment of individual attacks of angina pectoris. Quart. J. Med. **3**: 105, 1934.
10. Russek, H. I., Zohman, B. L., Drumm, A. E., Weingarten, W., and Dorset, V. J.: Long acting coronary vasodilator drugs: Metamine, Paveril, Nitroglyn, and Peritrate. Circulation **12**: 169, 1955.
11. Huppert, V. F. and Boyd, L. J.: Sustained-action nitroglycerin (Nitroglyn) in angina pectoris due to coronary sclerosis. Bull. New York M. Coll. **18**: 58, 1956.
12. Von Oettingen, W. F., Donahue, D. D., Lawton, A. H., Monaco, A. R., Yagoda, H. and Valaer, P. J.: Toxicity and potential dangers of penta-erythritol tetranitrate (PETN). Public Health Service Bulletin No. 282, U. S. Public Health Service, 1944.
13. —: The effects of aliphatic nitrous and nitric acid esters on the physiological functions with special reference to their chemical constitution. National Institute of Health Bulletin No. 186, U. S. Public Health Service, 1946.
14. Davis, J. A. and Wiesel, B. H.: The treatment of angina pectoris with a nitroglycerin ointment. Am. J. M. Sc. **230**: 259, 1955.
15. Hefner, L. L., Friedman, B., Reeves, T. J., Eddleman, E. E., and Harrison, T. J.: Symposium on coronary dilator drugs. Circulation **15**: 111, 1957.
16. Bradbury, J. B.: The Bradshaw lecture on some new vaso-dilators. Brit. M. J. **2**: 1213, 1895.
17. Krantz, J. C., Carr, C. J., Forman, S. E. and Ellis, F. W.: Alkyl nitrites. IV. The pharmacology of isomannide dinitrate. J. Pharmacol. & Exper. Therap. **67**: 191, 1939.
18. —, —, —, and Cone, N.: Alkyl nitrites. VI. A contribution to the mechanism of the action of organic nitrates. J. Pharmacol. & Exper. Therap. **70**: 323, 1940.
19. Boyer, N. A. and Green, H. P.: The effects of nitrites and xanthines on coronary inflow and blood pressure in anesthetized dogs. Am. Heart J. **21**: 199, 1941.
20. Levy, R. L., Bruenn, H. G. and Williams, N. E.: The modifying action of certain drugs (aminophyllin, nitrites, digitalis) upon the effects of induced anoxemia in patients with coronary insufficiency, with remarks on therapy. Am. Heart J. **19**: 639, 1940.
21. Spiegl, E. D., Riseman, J. E. F., and Freedberg, A. S.: Unpublished data.
22. Bjërlov, H.: Nitropent, ett nytt medel mot

angina pectoris. Svenska läk.-tidning. **40**: 694, 1943.

23. Balatre, P., Merlen, J. F. and Granjean, L.: Les esters nitres des polyalcools en therapeutic cardiovasculaire. Presse méd. **57**: 1067, 1949.
24. Dailheu-Geoffrey, P.: Action comparee de la pentanitrine (penta-erythrite tetranitree) et des autres vaso-dilateurs coronariens dans l'angine de poitrine; Etude de 258 cas personnels, dont 97 traites par la pentanitrine. Quest méd. **3**: 319, 1950.
25. Marche, J.: Le traintement des coronarites chroniques par les esters nitres des polyalcools. Fiches méd. **144**: 1, 1950.
26. Perlman, A.: A study of the therapeutic action and toxicity of pentaerythritol tetranitrate. Angiology **3**: 16, 1952.
27. Plotz, M.: Pentaerythritol tetranitrate: A new drug for the treatment of coronary insufficiency. New York State J. Med. **52**: 16, 1952.
28. Rosenberg, H. N. and Michelson, A. L.: The use of pentaerythritol tetranitrate in chronic coronary insufficiency. Am. J. M. Sc. **230**: 254, 1955.
29. Winsor, T. and Humphreys, P.: Influence of pentaerythritol tetranitrate (Peritrate) on acute and chronic coronary insufficiency. Angiology **3**: 1, 1952.
30. Weitzman, D.: Pentaerythritol tetranitrate in the treatment of angina. Brit. M. J. **2**: 1409, 1953.
31. Russek, H. I., Urbach, K. F., Doerner, A. A. and Zohman, B. L.: Choice of a coronary vasodilator drug in clinical practice. J. A. M. A. **153**: 207, 1953.
32. Rossi, B.: Clinical and electrocardiographic study of some cases of hypertension and angina pectoris treated with peritrate. Angiology **6**: 59, 1955.
33. Winsor, T. and Scott, C. C.: Further observations of the cardiovascular effects of pentaerythritol tetranitrate in animals and man. Am. Heart J. **49**: 414, 1955.
34. Talley, R. W., Beard, O. W. and Doherty, J. F.: Use of pentaerythritol tetranitrate (Peritrate) in treatment of angina pectoris. Am. Heart J. **44**: 866, 1952.
35. Kalmanson, F. M., Drenick, E. J., Binder, M. J. and Rosove, L.: Pentaerythritol tetranitrate in the treatment of angina pectoris: Clinical evaluation. Arch. Int. Med. **95**: 819, 1955.
36. Kory, R. C., Townes, A. S., Mabe, R. E., Dorris, E. R. and Meneely, G. R.: Drug evaluation in angina pectoris: Khellin, heparin, Peritrate. Am. Heart J. **50**: 308, 1955.
37. Pfeiffer, H.: Über die Wirkung von Trinitrat auf den menschlichen Kreislauf. Klin. Wchnschr. **28**: 304, 1950.
38. Merlen, J. F.: Action du biphosphate de trinitro-triethanolamine dans l'angine de poitre et l'arterite obliterante. Therapie **6**: 223, 1951.
39. Dailheu-Geoffrey, P.: Action due biphosphate de trinitro-triethanolamine dans l'angine de poitrine. Clinque **46**: 27, 1951.
40. Melville, K. I. and Lu, F. C.: Cardiovascular effects of triethanolamine trinitrate, an experimental study. Canad. M.A.J. **65**: 11, 1951.
41. Palmer, J. H. and Ramsey, C. G.: Triethanolamine trinitrate (Metamine) in the treatment of angina pectoris: A preliminary report. Canad. M.A.J. **65**: 17, 1951.
42. Fuller, H. L. and Kassel, L. E.: Metamine (triethanolamine trinitrate biphosphate), J.A.M.A. **159**: 1708, 1955.
43. Heller, E. M.: Triethanolamine trinitrate (Metamine) in the treatment of angina pectoris. Canad. M.A.J. **74**: 197, 1956.
44. Friend, D. G., O'Hare, J. P. and Levine, H. D.: Action of triethanolamine trinitrate in angina pectoris. Am. Heart J. **48**: 775, 1954.
45. Zoll, P. M., Norman, L. R. and Cassin, S.: The effects of vasomotor drugs and of anemia upon interarterial coronary anastomoses. Circulation **6**: 832, 1952.
46. Riseman, J. E. F. and Stern, B.: A standard exercise tolerance test for patients with angina pectoris on exertion. Am. J. M. Sc. **188**: 646, 1934.
47. Freedberg, A. S., Spiegl, E. D. and Riseman, J. E. F.: Effect of external heat and cold on patients with angina pectoris: Evidence for existence of a reflex factor. Am. Heart J. **27**: 611, 1944.
48. —, and Riseman, J. E. F.: Cobra venom in the treatment of angina pectoris. New England J. Med. **233**: 462, 1945.
49. Stearns, S., Riseman, J. E. F. and Gray, W.: Alcohol in the treatment of angina pectoris. New England J. Med. **234**: 578, 1946.
50. Gray, W., Riseman, J. E. F. and Stearns, S.: Papaverine in the treatment of coronary artery disease. New England J. Med. **232**: 389, 1945.
51. Riseman, J. E. F., Waller, J. V. and Brown, M. G.: The electrocardiogram during attacks of angina pectoris, its characteristics and diagnostic significance. Am. Heart J. **19**: 683, 1940.
52. Brown, M. and Riseman, J. E. F.: The comparative value of purine derivatives in the treatment of angina pectoris. J.A.M.A. **109**: 266, 1937.
53. Wolff, H. G.: The cerebral circulation. XIC.

The action of amyl nitrite. Arch. Neurol. & Psychiat. **22**: 695, 1929.

54. Leake, C. D., Kammer, A. G. and Hitz, J. B.: Quantitative measurements on the dilatation of pial blood vessels after the administration of nitrites in dogs. J. Pharmacol. & Exper. Therap. **35**: 143, 1929.
55. Crandall, L. A., Jr., Leake, C. D., Loevenhart, A. S. and Muehlberger, C. W.: Acquired tolerance to and cross tolerance between the nitrous and nitric acid esters and sodium nitrite in man. J. Pharmacol. & Exper. Therap. **41**: 103, 1931.
56. Wood, H. C., Jr.: Art. II. Experimental researches on the physiological action of nitrite of amyl. Am. J. M. Sc. **62**: 39, 1871.
57. Reichert, E. T. and Weir Mitchell, S.: On the physiological action of potassium nitrite. Am. J. M. Sc. **80**: 158, 1880.
58. Loeb, R. F., Bock, A. V. and Fitz, R.: Acute nitrobenzol poisoning with studies on the blood in two cases. Am. J. M. Sc. **161**: 539, 1921.
59. Van Slyke, D. D. and Vollmund, E.: Studies of methemoglobin formation. J. Biol. Chem. **66**: 415, 1925.
60. Krantz, J. C., Jr., Carr, C. J. and Forman, S. E.: Alkyl nitrites. II. The pharmacology of 2-ethyl -N-hexyl -nitrite. J. Pharmacol. & Exper. Therap. **64**: 302, 1938.
61. Rabinowitch, I. M.: Acute nitroglycerin poisoning. Canad. M.A.J. **50**: 199, 1944.
62. Rath, M. and Krantz, J. C.: Nitrites. IX. A further study of the mechanism of the action of organic nitrates. J. Pharmacol. & Exper. Therap. **76**: 33, 1942.
63. Drabkin, D. L. and Austin, H. J.: Spectrophotometry of hemoglobin. J. Biol. Chem. **98**: 719, 1932.
64. Evelyn, K. A. and Malloy, H. T.: Microdetermination of oxyhemoglobin, methemoglobin and sulfhemoglobin in a single sample of blood. J. Biol. Chem. **126**: 655, 1938.
65. Horecker, B. L. and Brackett, F. S.: A rapid spectrophotometric method for the determination of methemoglobin and carbonylhemoglobin in the blood. J. Biol. Chem. **152**: 669, 1944.
66. Greenberg, M., Birnkrant, W. and Schiftner, J. J.: Outbreak of sodium nitrite poisoning. Am. J. Pub. Health **35**: 1217, 1945.
67. Padberg, L. R. and Martin, T.: Three fatal cases of sodium nitrite poisoning. J.A.M.A. **113**: 1733, 1939.
68. Bresler, R. R.: Nitroglycerin reactions among pharmaceutical workers. Indust. Med. & Surg. **18**: 519, 1949.
69. Proger, S. H. and Ayman, D.: Harmful effects of nitroglycerin with special reference to coronary thrombosis. Am. J. M. Sc. **184**: 480, 1932.
70. Sprague, H. B. and White, P. D.: Nitroglycerin collapse, a potential danger in therapy. Report of three cases. M. Clin. North America **16**: 895, 1933.
71. White, P. D.: The significance and treatment of cardiac symptoms. New England J. Med. **205**: 907, 1931.
72. Jacobson, S. M.: Unusual reaction to glyceryl trinitrate. Southern M. J. **49**: 936, 1950.

Endocardial Fibroelastosis

Angiocardiographic Studies

By Leonard M. Linde, M.D., Forrest H. Adams, M.D., and Bernard J. O'Loughlin, M.D.

Endocardial fibroelastosis is an important cause of congestive heart failure and death in infancy and early childhood. Four cases of this entity are described, with particular attention to the unique angiocardiographic features. This graphic portrayal of the functional derangement may be of great help in the clinical diagnosis of fibroelastosis.

ENDOCARDIAL fibroelastosis as a cause of severe cardiac hypertrophy in infants is being recognized with increasing frequency. The diagnosis can be suspected clinically,[1] but final confirmation must be made at necropsy. This report describes an angiocardiographic sign that may be helpful in the antemortem diagnosis of this entity and that may help us to understand better its pathologic physiology.

Method

Four children were studied in whom the chronic form of primary endocardial fibroelastosis was diagnosed clinically. In one of these patients the diagnosis was confirmed at autopsy. In addition to the routine clinical and laboratory procedures, cardiac catheterization and selective angiocardiography were performed on the 4 patients. Biplane angiocardiograms were taken at 6 or 12 frames per second after automatic injection at 5 Kg./cm.^{2} of 50 per cent sodium diprotrizoate (Miokon*) into the main pulmonary artery. Mechanical systole and diastole were determined by inspection and confirmed by reference to simultaneously recorded electrocardiograms.

Results

The angiocardiograms in these patients with endocardial fibroelastosis uniformly showed greatly diminished left ventricular contractility. In 3 patients there was no change in systolic and diastolic volume in consecutive cardiac cycles. Angiocardiography in the fourth patient, performed prior to the development of cardiovascular symptoms, showed slight cyclic changes in the cardiac contour. All studies demonstrated prolonged retention of dye in an enlarged left ventricle.

Case Report

Case 1. C. L. B., a white girl, developed dyspnea, listlessness, vomiting, and pallor at 3½ months of age. (A male sibling had died at age 3½ months with identical symptoms, but no diagnostic or postmortem studies had been performed.) Examination revealed rapid grunting respiration and faint heart tones without a murmur. Congestive heart failure was diagnosed and responded to therapy. The electrocardiogram showed marked left ventricular hypertrophy. A roentgenogram demonstrated gross cardiomegaly involving the left ventricle and left atrium. On cardiac catheterization there were normal right heart pressures, oxygen saturations consistent with decreased cardiac output, and no evidence of left-to-right shunt (table 1). The angiocardiogram showed a large left ventricular cavity with an unchanging contour during systole and diastole and prolonged retention of dye (fig. 1).

In spite of radiation therapy to the heart and general supportive measures, the patient's condition progressively deteriorated, with fatal heart failure occurring at age 2 years. At postmortem examination a 2-mm. thick, yellow-white endocardium coated the left atrium, left ventricle, and mitral valve. There was biventricular hypertrophy and dilatation with congestion related to left and right heart failure. No other cardiac anomalies were found.

Case 2. D. V. W., a 4½-month-old white boy, previously reported,[2] suddenly developed rapid respirations, irritability, pallor, anorexia, and vomiting. Examination revealed a pale infant in shock, with gross cardiomegaly and marked hepatomegaly. Heart tones were muffled and no murmurs were audible. He improved after appropriate treatment of the shock and congestive heart failure. Electrocardiograms showed left ventricular hypertrophy with inverted T waves over the left precordium. A roentgenogram revealed marked cardiac enlargement, mainly left ventricular, with some left atrial enlargement. The findings on cardiac catheterization were within normal limits (table 1). The

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* Manufactured by Mallinckrodt Chemical Works, St. Louis, Mo.

angiocardiogram showed loss of left ventricular contractility with diminished expulsion of dye (fig. 2).

When last seen at 13 months of age, pallor, rapid respirations and cardiomegaly persisted, but the patient's condition was stable with maintenance digitalis therapy.

Case 3. C. B., a 2-year-old white girl, had an enlarged heart at age 19 months on a roentgenogram that was taken during an episode of pneumonia. For 2 months prior to entry her private physician heard a cardiac murmur intermittently. Examination revealed cardiac enlargement with heart tones of fair quality. A short soft midsystolic murmur in the left second interspace and a higher pitched localized apical systolic murmur were barely audible. The electrocardiogram was consistent with left ventricular hypertrophy. On chest roentgenogram there was moderately severe cardiomegaly involving the left ventricle and left atrium. Cardiac catheterization revealed normal right heart pressures, low oxygen saturations consistent with low cardiac output, and no evidence of left-to-right shunt (table 1). The

TABLE 1.—*Cardiac Catheterization in Four Patients with Primary Endocardial Fibroelastosis*

Case no.	Pressure mm. Hg			Oxygen saturation %				
	Right atrium	Right ventricle	Pulmonary artery	Vena cava	Right atrium	Right ventricle	Pulmonary artery	Femoral artery
1	3/1	21/3	21/13	63	60	65	64	85
2	7/3	27/0	27/17	77	75	75	75	—
3	7/4	26/4	26/16	64	55	57	58	89
4	8/1	43/1	34/18	62	56	55	56	92

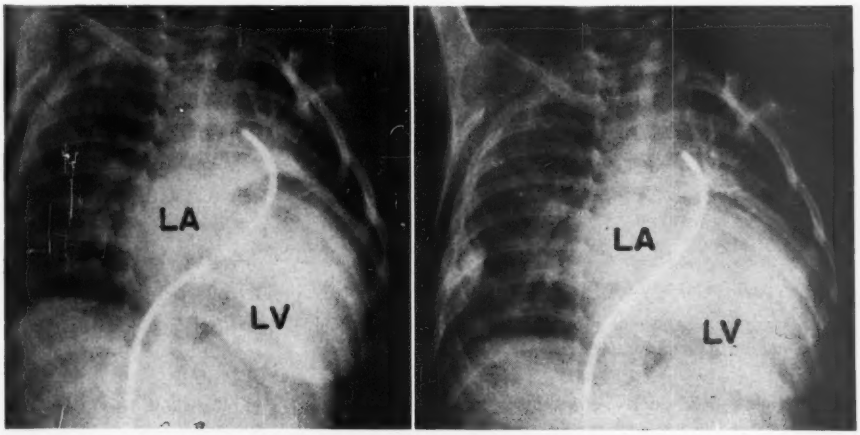

FIG. 1. Case 1. Angiocardiogram with dye in the left heart shows no measurable change in ventricular volume in systole (*right*) and diastole (*left*). Atrial change is less than normal.

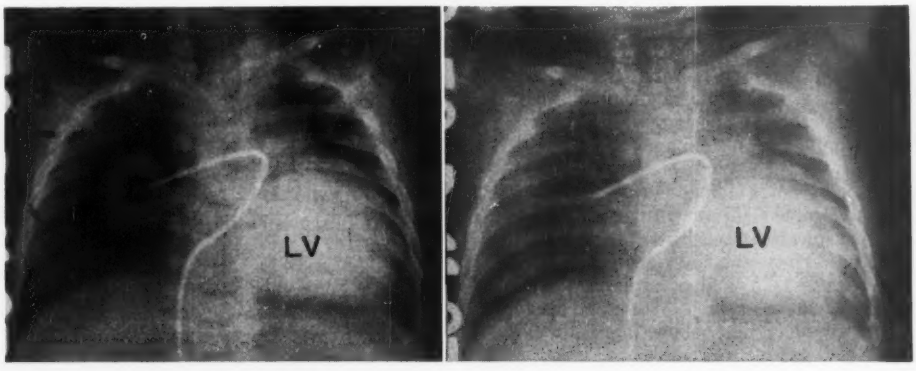

FIG. 2. Case 2. Angiocardiogram demonstrating unchanging left ventricular volume and poor aortic filling.

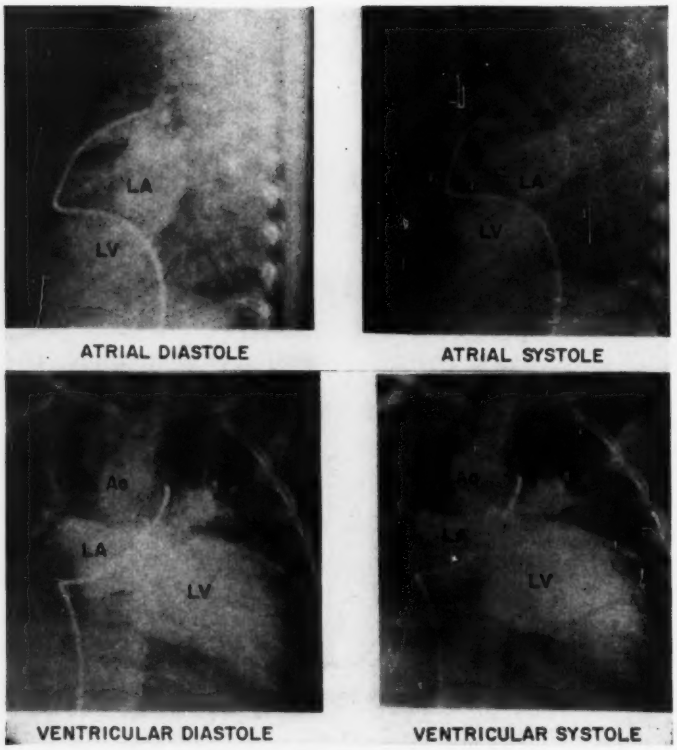

FIG. 3. Case 3. Lateral and anteroposterior angiocardiographic views depicting absent left ventricular contractility and reduced left atrial contractility.

angiocardiogram showed a poorly emptying, enlarged left ventricle with an unchanging contour (fig. 3).

Case 4. M. G., a 6-month-old white boy, had cardiac enlargement on a roentgenogram taken because of "repeated colds, chest congestion, and rapid breathing." Examination revealed a rapid respiratory rate. Cardiomegaly was associated with a loud high-pitched apical systolic murmur, transmitted to the left axilla. Electrocardiographic findings consisted of left ventricular hypertrophy with inverted T waves over the left precordium. An enlarged left ventricle was the main cause of the cardiomegaly seen on the chest film. Findings on cardiac catheterization were elevated right ventricular pressure and low oxygen saturations consistent with decreased cardiac output. There was no evidence of a left-to-right shunt (table 1). The angiocardiogram demonstrated reduced but measurable systolic and diastolic variation in left ventricular volume (fig. 4).

DISCUSSION

The clinical aspects of endocardial fibroelastosis have been covered in an excellent extensive review of the subject by Dennis and coworkers.[3] Suspected etiologic agents have been numerous[4-12] but the final result is a thickened endocardium that limits expansion and contraction of the ventricle. This splinting action leads to heart failure in most patients.

Others have described the radiologic picture[13] to consist of great cardiomegaly, predominantly of the left ventricle. On angiocardiography left ventricular enlargement and delayed systolic expulsion have been described.[14-17]

In our experience reciprocal atrial and ventricular filling is easily seen in normal patients (fig. 5) and in patients with cardiac conditions other than endocardial fibroelastosis (figs. 5 and 6). Atrial systole accompanies ventricular diastole, while atrial filling occurs simultaneously with ventricular emptying. Figure 5 shows the respective chamber emptying to be fairly complete in the normal, with marked

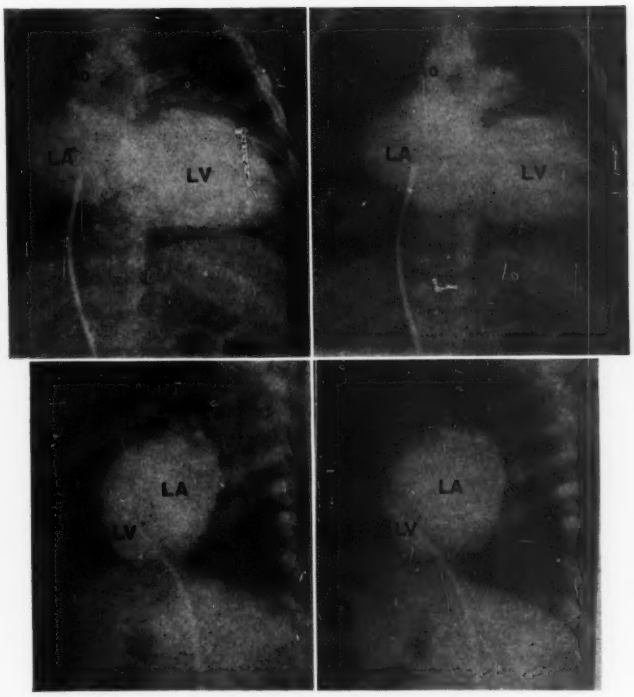

FIG. 4. Case 4. Anteroposterior angiocardiogram (*upper films*) demonstrates greatly reduced systolic (*right films*) and diastolic (*left films*) volume change in the left ventricle and left atrium. On the lateral views (*lower films*) aortic filling is seen with ventricular systole.

change in systolic and diastolic volume during the cardiac cycle.

This is in sharp contrast to what is seen in patients with endocardial fibroelastosis (figs. 1–4). In such patients, no systolic and diastolic change in volume occurs. Dye enters an enlarged left ventricular cavity and remains there, as muscular contraction is apparently impaired by a splinting action of the thickened endocardium. In case 4, studied when he had few cardiovascular symptoms, minimal systolic and diastolic change occurred. Perhaps this instance represented an early stage in the development of the typical angiocardiogriaphc picture.

Angiocardiographic studies were also performed in patients with left ventricular enlargement and left ventricular failure without endocardial fibroelastosis. Figure 6 shows marked systolic and diastolic change in volume on the angiocardiogram of a patient with a ventricular septal defect, left ventricular hypertrophy, and left ventricular failure.

Before the specificity of this interesting angiocardiographic sign can be fully evaluated, studies must be performed on the other rarer types of heart disease formerly classified as "idiopathic cardiac hypertrophy." Glycogen storage disease of the heart, aberrant left coronary artery disease, and idiopathic myocarditis can all clinically resemble endocardial fibroelastosis, but at the present time we have not studied patients with these other diseases angiocardiographically. It is hoped, however, that patients with an aberrant left coronary artery will be recognized by the technic of injecting the radiopaque material selectively into the main pulmonary artery. If such a vessel is present, it should be well seen in the lateral view originating from the main pulmonary artery.

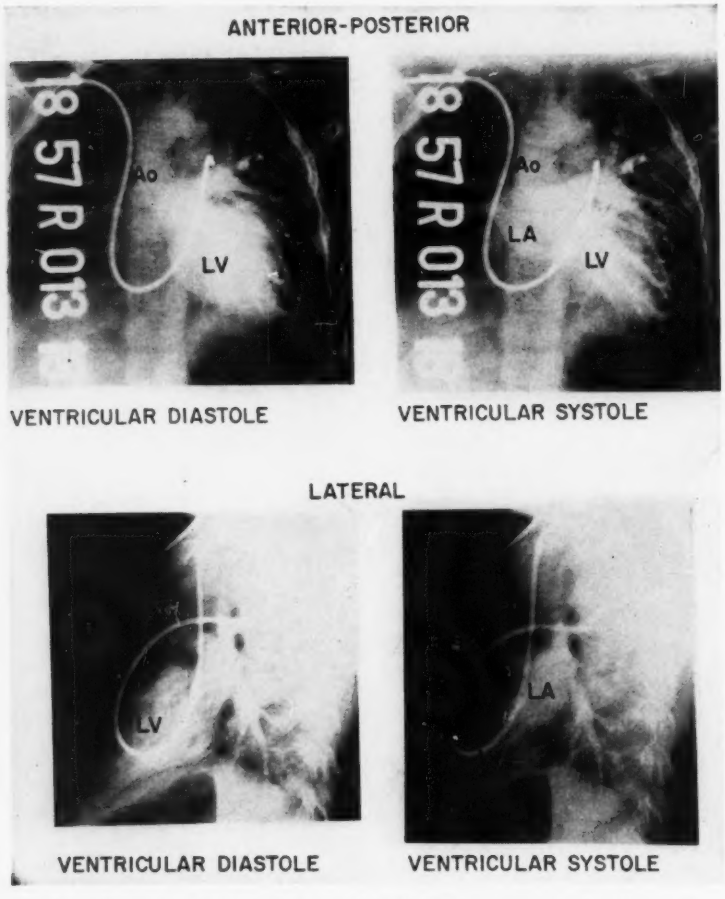

FIG. 5. Angiocardiogram of a normal 6-year-old girl. The anteroposterior (*upper films*) and lateral (*lower films*) views show marked left ventricular change in volume and reciprocal atrial variation in systole and diastole.

SUMMARY

Selective biplane angiocardiography was performed in 4 patients with the chronic form of primary endocardial fibroelastosis. The diagnosis was made clinically in all and confirmed at autopsy in 1. A striking finding was the unchanging size and contour of the left ventricle. Evidence was presented to indicate that this was not due to heart failure or left ventricular hypertrophy. These observations may help in understanding the pathologic physiology in endocardial fibroelastosis and may be of aid in the antemortem diagnosis of this entity.

SUMMARIO IN INTERLINGUA

Selective angiocardiographia biplan esseva executate in 4 patientes con le forma chronic de primari fibroelastosis endocardial. Le diagnose esseva facite clinicamente in omne casos e confirmate al necropsia in 1. Un constatation frappante esseva le nonalterate dimension e contorno del ventriculo sinistre. Es documentate le these que isto non resultava de disfallimento cardiac o hypertrophia sinistroventricular. Iste observationes va possibilemente promover le comprension del pathophysiologia de fibroelastosis endocardial e

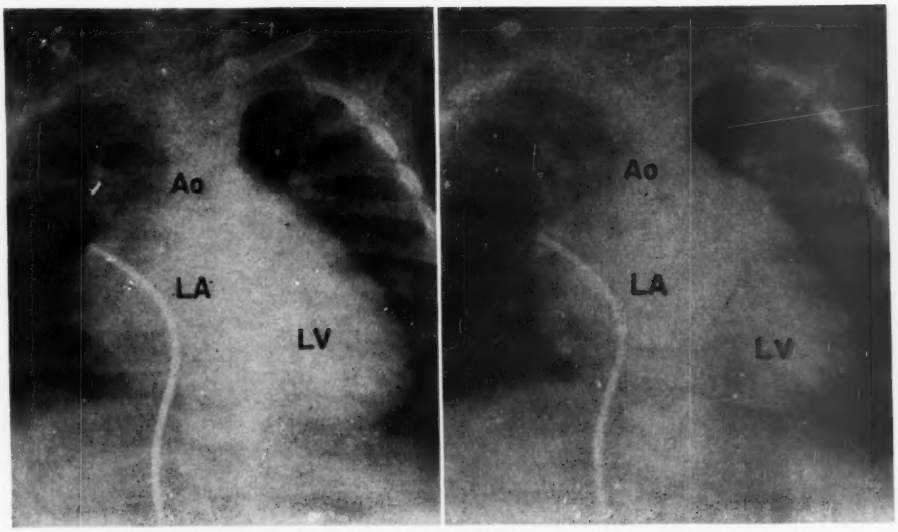

FIG. 6. Angiocardiogram in patient with ventricular septal defect and left heart failure. It shows an enlarged left ventricle (*left film*) and complete systolic dye expulsion (*right film*). Atrial volume change is also seen.

assister in establir le diagnose de iste entitate ante le morte.

REFERENCES

[1] ADAMS, F. H., AND KATZ, B. E.: Endocardial fibroelastosis: Case reports with special emphasis on the clinical findings. J. Pediat. **41:** 141, 1952.

[2] MCFALL, R. A. AUSTIN, W. O., ADAMS, F. H., AND O'LOUGHLIN, B. J.: Selective angiocardiography in congenital heart disease. California Med. **86:** 162, 1957.

[3] DENNIS, J. L., HANSEN, A. E., AND CORPENING, T. M.: Endocardial fibroelastosis. Pediatrics **12:** 130, 1953.

[4] HILL, W. T., AND REILLY, W. A.: Endocardial fibroelastosis. Am. J. Dis. Child. **82:** 579, 1951.

[5] JOHNSON, F. R.: Anoxia as the cause of endocardial fibroelastosis in infancy. Arch. Path. **54:** 237, 1952.

[6] ULLRICH, O.: Angeborene Herzhypertrophie mit Endokardfibrose bei zwei eineiigen Partnern von mannlichen Drillingen. Ztschr. menschl. Vererb. u. Konstitutionslehre **21:** 585, 1938.

[7] WEINBERG, T., AND HIMMELFARB, A. J.: Endocardial fibroelastosis (so-called fetal endocarditis): A report of 2 cases occurring in siblings. Bull. Johns Hopkins Hosp. **72:** 299 1943.

[8] GREAVES, J. L., WILKINS, P. S. W., AND PEARSON, S.: Endocardial fibroelastosis in identical twins. Arch. Dis. Childhood **29:** 447, 1954.

[9] CARTER, B.: Personal communication, as quoted by Greaves et al. (ref. 8).

[10] ROSAHN, P. O.: Endocardial fibroelastosis: Old and new concepts. Bull. New York Acad. Med. **31:** 453, 1955.

[11] ANDERSEN, D. H., AND KELLY, J.: Endocardial fibroelastosis: I. Endocardial fibroelastosis associated with congenital malformations of the heart. Pediatrics **18:** 513, 1956.

[12] KELLY, J., AND ANDERSEN, D. H.: Congenital endocardial fibroelastosis: II. A clinical and pathological investigation of those cases without associated cardiac malformations including report of two familial instances. Pediatrics **18:** 539, 1956.

[13] EYLER, W. R., ZIEGLER, R. F., SHEA, J. J., AND KNABE, G. W.: Endocardial fibroelastosis: Roentgen appearance. Radiology **64:** 797, 1955.

[14] MANNHEIMER, F., BENGTSSON, E., AND WINBERG, J.: Pure congenital mitral stenosis due to fibroelastosis. Cardiologia **21:** 574, 1952.

[15] PREC, K. J., AND CASSELS, D. E.: Functional aspects of congenital defects affecting the left ventricle. J. Pediat. **41:** 451, 1952.

[16] GASUL, B. M., WEISS, H., FELL, E. H., DILLON, R. F., FISHER, D. C., AND MARIENFELD, C. J.: Angiocardiography in congenital heart disease correlated with clinical and autopsy findings. Am. J. Dis. Child. **85:** 404, 1953.

[17] ABRAMS, H. L., AND KAPLAN, H. S.: Angiocardiographic Interpretation in Congenital Heart Disease. Springfield, Ill., Charles C Thomas, 1956, p. 215.

Comparison of Four Orthogonal Systems of Vectorcardiography

By PAUL H. LANGNER, JR., M.D., ROBERT H. OKADA, PH.D., SAMUEL R. MOORE, M.D., AND HARRY L. FIES

Four orthogonal systems of vectorcardiography that are considered to be more accurate than the tetrahedron and cube systems were compared. In a large majority of subjects the records made with each of the 4 systems were similar. However, in 5 of 60 subjects in whom the Z lead was studied, dissimilarities were found that were considered to be significant. The possible reasons for these dissimilarities are discussed. Comparative normalization data for the systems were obtained in the living human subject, based upon comparison of wave forms.

RECENTLY 4 systems of vectorcardiography based on well-established principles of potential theory have been devised by Schmitt and Simonson,[1] Frank,[2] McFee and Johnston,[3] and Helm.[4] They each attempt to provide a more orthogonal reference frame than the cube and the tetrahedron systems. It is the purpose of this paper to report the results of a comparative study in the living human subject of these 4 systems. The study was undertaken for 2 reasons, to determine how interchangeable the results of the different systems were and to provide comparative normalization data for each system in the living subject. If the systems yielded similar results, the study would serve as a consistency check on the validity of the separate methods of analysis and synthesis.

METHOD

The 3 leads of each orthogonal reference frame were compared individually. They were paired with a common lead to produce a loop rather than being recorded as scalar leads. The latter method requires high-speed, dual-channel recording with a common lead for phase relations, and analysis of such records was found to be less obvious and informative.

All studies were performed with the subject recumbent. Loops were observed directly on an oscilloscope and photographed with a Polaroid Land camera. Each comparison of 4 different X, Y, and Z leads required 2 experimental sessions totaling about 4 hours. Experiments were repeated on different days in 10 instances for the Z lead and 3 for the Y. No X lead studies were repeated because of uniformly good agreement among the 4 types.

Z Lead. Since the anteroposterior or Z lead has been the most variable component in existing systems of vectorcardiography, the major portion of this study was devoted to it. The Z lead of each system was paired consecutively with a common X lead (Schmitt system), and the gain of the Z channel controlled so that the peak-to-peak excursion was the same for all loops. The gain was then recorded for normalization information. The Z leads of the Frank and the Schmitt SVEC III systems were employed as described by these authors in their original communications.[1, 2] The sponge electrode of Helm[4] and the multiple bank of electrodes of McFee and Johnston[3] are described as follows.

The sponge electrode consisted of a thin plastic sponge moistened with a saturated solution of sodium chloride. Two sizes of sponge were used on the anterior chest wall to record the Z lead. A large sponge 10 inches square was positioned to cover the area from the first to the seventh interspace and from approximately the right midclavicular line to a line between the V_4 and V_5 positions. A smaller sponge with dimensions of 8½ inches from right to left and 6½ inches from top to bottom was placed on the precordium, extending from the level of the second to the sixth rib and from V_1 to a line between the V_4 and V_5 positions. The sponge electrode was applied first at the beginning of each experiment without skin preparation, such as rubbing or defatting, and secured in place with a flat sandbag. To complete the Z lead a single electrode 1 inch in diameter was paired with either sponge electrode and placed on the back as recommended by Helm.[4] Connection was made at the upper outer edge of the sponge by means of an alligator clip insulated from the skin.

The multiple electrode consisted of a 6 by 5 matrix of ½-inch diameter electrodes, spaced 1½

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inches apart in both directions, and set in a sponge rubber mat. Each electrode was connected to a common terminal through a separate 1-megohm resistor. The over-all area spanned by the electrodes was 8½ inches by 6½ inches, the same area as that of the smaller sponge. To record the Z lead the bank of electrodes was placed on the subject with the larger side horizontally, and in the average individual covered an area from the level of the second to the sixth rib and from the V_1 precordial electrode site to a line between the V_4 and V_5 positions. The skin was defatted by rubbing with an alcohol-ether mixture. Then a small amount of jelly was placed on each electrode avoiding spread beyond the electrode surface. After the assembly was secured in place with a sandbag, each electrode circuit was checked for contact resistance with an ohm meter. Good contact was further attested to by the fact that an imprint of each electrode was seen in the skin after the matrix was removed. A smaller multiple electrode, consisting of a 5 by 4 matrix of electrodes covering an area 6½ by 5½ inches, was centered on the back behind the anterior electrode to complete the Z lead.

X Lead. For study of the X lead, either a constant Z or Y lead was paired consecutively with different X leads. The X leads of the Frank and Schmitt systems were employed as described by the authors in their original publications, with the one exception that the Frank electrodes were placed at the fourth interspace. The X lead originally suggested by McFee and Johnston was omitted because it was so similar to the Schmitt X lead. Instead, the smaller multiple type electrode was placed in the left axilla, extending from a line between the V_4 and V_5 positions to approximately the posterior axillary line and from armpit to the sixth or seventh rib. This was paired with a single electrode 1 inch in diameter, placed at the right anterior axillary line in the fourth interspace. The sponge type X lead consisted of a sheet of plastic sponge 8½ by 6½ inches, similarly positioned in the left axilla, paired with a single electrode on the right. In the 24 studies of the X lead only 10 experiments with the sponge electrode were done because the results were so similar to those using the multiple electrode.

Y Lead. The Y leads of Schmitt, Frank, and Helm were used as originally described. It was our interpretation of recommendations by McFee and Johnston that an average Burger triangle could be used for the derivation of the Y lead. Inspection of image space diagrams reveals that the orientation of lead aV_F derived from an average Burger triangle is so similar to the conventional aV_F with equal resistors that we used the latter as a matter of convenience.

Material

For comparison of the Z leads, transverse plane vectorcardiograms of 60 subjects were recorded. Twenty-seven subjects were considered normal, being free from symptoms, signs, or history of cardiovascular disease and having normal electrocardiograms and chest x-rays. Of 33 abnormal subjects there were 13 with right bundle-branch block, 4 with left bundle-branch block, 8 with the electrocardiographic pattern of myocardial ischemia, 3 with healed myocardial infarction and residual Q waves, 3 with the pattern of left ventricular hypertrophy, and 2 with abnormal P-R intervals. Sixteen subjects with bundle-branch block were asymptomatic and without other evidence of heart disease. The heart size was well within limits of normal variation in all but 6 of the abnormal group. In 3 the cardiothoracic ratio was just 50 per cent and in 3 more it was approximately 55 per cent. One subject in this latter group showed poor matching as illustrated in figure 4.

In the X-lead study 11 subjects were normal and 13 had various electrocardiographic abnormalities, including 5 with right bundle-branch block, 3 with left bundle-branch block, and 5 with the pattern of myocardial ischemia.

In the Y-lead study 10 subjects were normal, 1 had right bundle-branch block, and 2 had the pattern of myocardial ischemia.

Results

In a large majority of subjects, the X, Y, and Z leads of the 4 systems were similar in contour. Since comparison of loops has thus far defied precise quantitative analysis, results were graded subjectively in 3 classes according to their degree of similarity. Examples of each class are shown in figures 1 through 4. Classification of the records derived for the Z lead is shown in tables 1 and 2. Only in group III were the differences considered of possible diagnostic significance, as interpretable by present methods. In all subjects the direction of rotation of the loops was the same in all 4 systems.

For the 60 subjects in whom the Z leads of the 4 systems were compared the results were as follows. In all 27 normal subjects the QRS loop comparison was classified as group I or II, and the T as group I or II in 25 cases and group III in 2 cases. In the abnormal group of

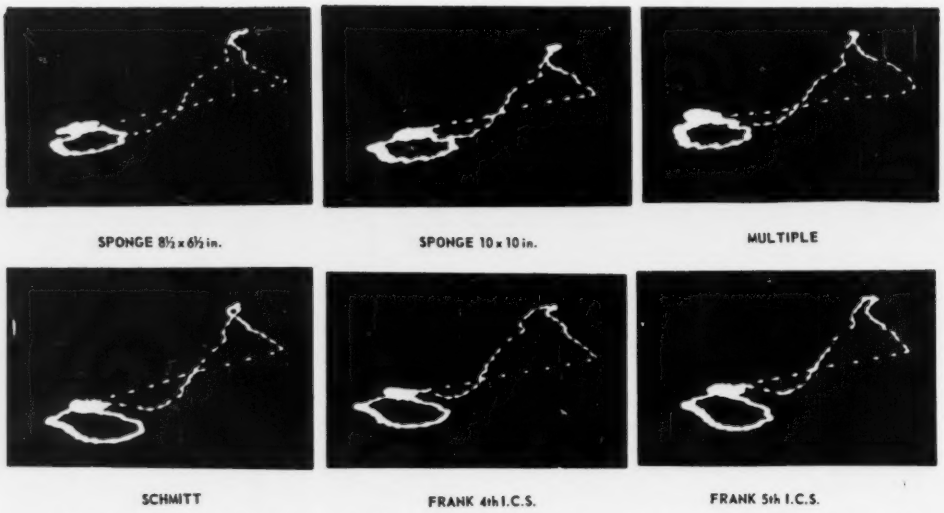

FIG. 1. Excellent similarity in matching of loops for the various Z leads. The Z lead goes from the bottom to the top of the picture and the X lead, which was the same in each instance, from right to left. Although there are minor variations, the similarity is remarkable, especially in view of the fact that this is a left bundle-branch block. An example of a group I classification.

33 subjects the QRS was classified as group I or II in 28 cases and group III in 5 cases. The T wave in the abnormal group was group I or II in 30 subjects and group III in 3 subjects (table 2).

Right bundle-branch block was the pattern that gave the poorest matching of loops, (figs. 3 and 4). Four subjects with this pattern were classified as group III. However, in 9 other subjects with right bundle-branch block the loops were similar. In the records with dissimilar loops the diagnosis of right bundle-branch block can be made. However, if the vectorcardiogram becomes a truly quantitative diagnostic procedure so that right bundle-branch block can be subdivided regarding type or degree, and the interrelationship of the QRS and T loops becomes more meaningful, the variation among these loops as illustrated in figures 3 and 4 could be of significance.

The 10 by 10-inch and the 8½ by 6½-inch sponges were compared in 33 of the 60 Z-lead studies. Occasional moderate differences were encountered. In 8 subjects the large sponge was in better agreement with the other 3 systems.

With regard to the Frank system, electrodes were placed at both the fourth and fifth interspaces in 53 subjects. In 7 instances records taken at the fifth interspace differed significantly from those taken at the fourth, while the latter were in good agreement with the other 3 systems.

X leads were compared in 24 subjects. The results were all group I or II. Figure 5 shows a comparison of 4 different X leads. The similarity of the loops in this instance is very good and this was considered a group I result.

Figure 6 shows a comparison of Y leads of 4 types, those recommended by Schmitt, Frank, and Helm, and aV_F. This phase of the study was limited to 13 experiments because of the similarity of the results and because it was believed that the Y lead was a comparatively simple problem, being a head-to-foot lead with refinements that would not be expected to have any profound influence. Figure 6 is an example of the poorest result. In 3 of 13 instances, aV_F showed this degree of dissimilarity while the other systems were in good agreement.

Results of comparative lead magnitudes were available for 47 subjects for the Z lead, 24

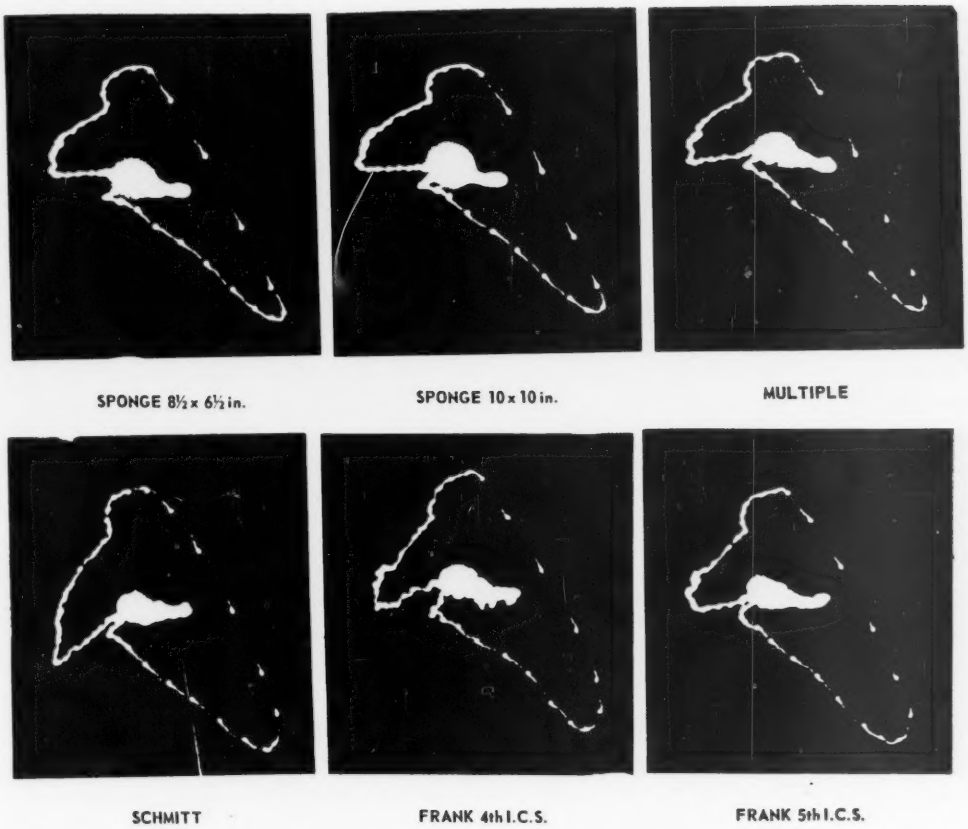

FIG. 2. Good similarity in matching of loops for the Z lead. Except for the Schmitt lead which shows moderate deviation, the other loops are similar. This subject had right bundle-branch block. An example of a group II classification. Directions of X and Z leads are the same as in figure 1.

for the X, and 10 for the Y. Only group I and II results were used for this calculation.

With the Schmitt system as a reference, the relative magnitudes of all lead vectors are listed in table 3. The Schmitt system requires normalization external to the electrode system to equalize the lead vectors. The Frank system has normalization built into its resistor network and the results indicate excellent consistency with the Schmitt system for X and Z and a difference in Y leads of 13 per cent of the mean. The results for the Helm system show excellent agreement with the Schmitt system for Z and Y and a difference in the X lead of 17 per cent of the mean.

DISCUSSION

An important problem in vectorcardiography is the choice of a practical system of electrode placement that will provide a frame of reference consisting of 3 mutually perpendicular lead vectors of equal length. It has been demonstrated that there may be considerable variation in the same individual between vectorcardiograms made with the cube and the tetrahedral method of electrode placement[5-8] and this would be expected on the basis of model studies.[1, 9] Recently, 4 systems of electrode placement based on more accurate theoretical and experimental grounds have been devised. The systems employ multiple

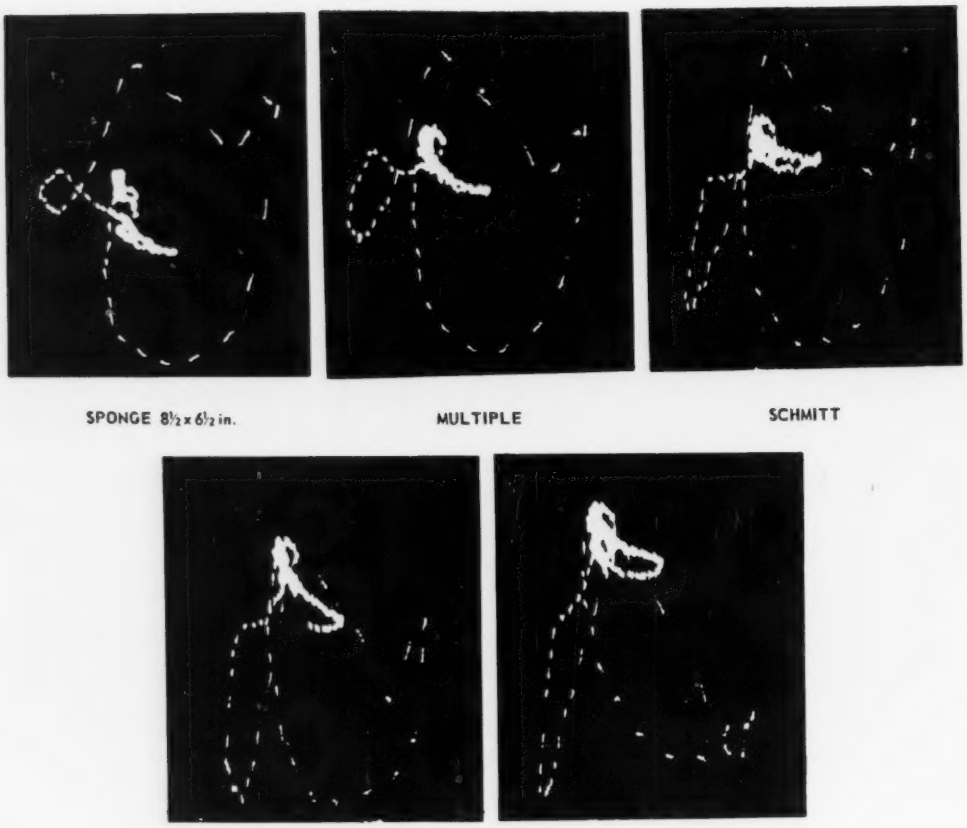

FIG. 3. Poor matching of the loops in a subject with right bundle-branch block. There is considerable variation in the terminal appendage of the loop. The rest of the loop is fairly similar in the sponge, multiple, and Schmitt systems. There is greater variation in the Frank Z recorded in the fourth interspace and poor correspondence in the case of the Frank Z recorded at the fifth interspace. An example of a group III classification. Direction of X and Z leads is the same as in figure 1.

electrode sites and computing networks, which either compensate for variations in heart dipole location within a given region or give equal weighting to any dipoles located in this given region. These statements are equivalent.

However, it is fundamental to recognize that because of this compensating and weighting these systems attempt to yield information only about the dipole component of the actual heart generator. Indeed, if the heart's electric activity cannot be completely accounted for by the action of an equivalent dipole in a homogeneous medium, these systems cannot by themselves yield all the available information. When the dipole component does not represent the total heart activity, these systems suppress the nondipole information. In this case additional information is available, for example, in precordial scalar leads.

The 4 systems are quite different, and each was arrived at through a somewhat different theoretical approach. All are based on results of model studies. Frank's and Schmitt's studies were performed on 3-dimensional homogeneous torso models whereas McFee and Johnston used only 2-dimensional models.

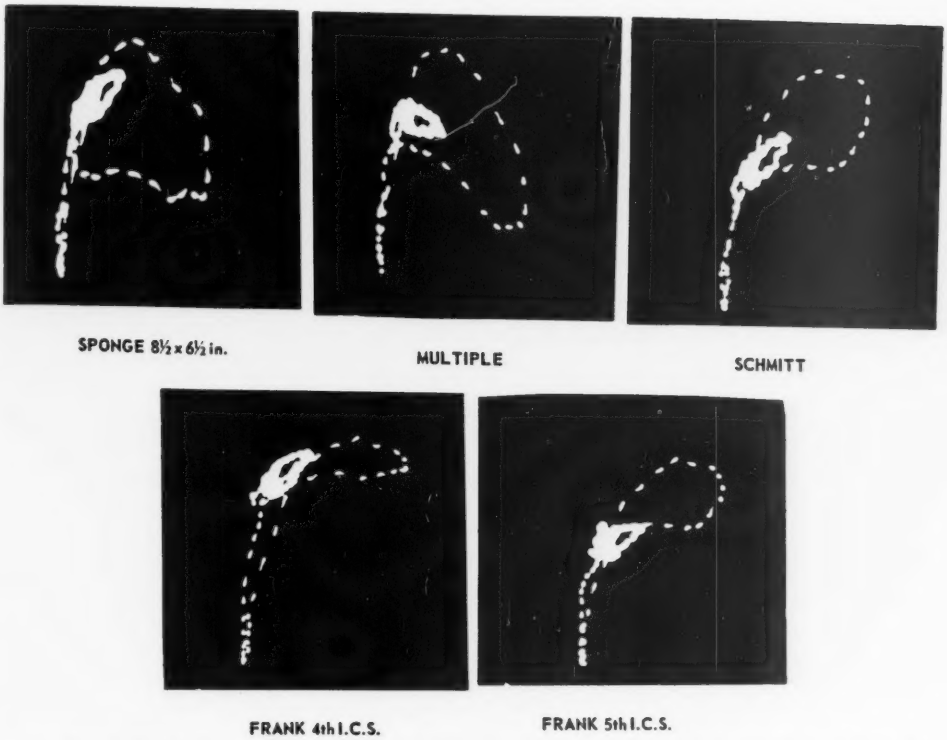

FIG. 4. Illustration of another group III classification in a subject with right bundle-branch block. This is a decidedly poor match. The terminal appendage of each loop can be matched fairly well but there is poor correspondence with the rest of the loop and with the direction of the T wave from one system to another. Direction of X and Z leads is the same as in figure 1.

Helm derived his system from the model data published by Frank. The theoretical basis for each system is as follows. Frank used image surface representation to derive his system, which is reasonably accurate for a dipole located within a 5- by 5- by 5-cm. volume, provided the electrode level is placed in the plane of possible dipole location. Schmitt used transfer impedance representation to derive his system, which is reasonably accurate for one or more dipoles located within a 5- by 5- by 5-cm. volume in the anatomic region of the heart. McFee and Johnston used the lead field or reciprocal field concept to derive their system. Normalization figures and limits of accuracy of the latter system have not been stated. Helm used Frank's model results to derive his system by mathematical analyses. Using any of these 3 tools of analysis and synthesis, namely, image surface, transfer impedance, or reciprocal field, one can explain equally well each of these systems. For linear resistive media there is a one-to-one correspondence between these tools and no one is fundamentally more general than the others.

Briefly, the advantages and disadvantages of each system are as follows. The Frank system is simplest to apply and has the advantage that precordial electrodes are already in place if it is desired to record scalar leads. However, the chief disadvantage of the Frank system is vulnerability in the event that electrodes are not placed at the mean electric heart center level. The sponge electrode is very inexpensive and simple to apply. However, despite the relative agreement between the sponge and the multiple electrode in all but 2 of 60 individuals there is still some reservation about the

TABLE 1.—*Results of Z-Lead Shape Comparisons of Four Different Systems in Normal Subjects*

Loop	Group I	Group II	Group III	Total cases
QRS	13	14	0	27
T	16	9	2	27

TABLE 2.—*Results of Z-Lead Comparisons of Four Different Systems in Abnormal Subjects*

Group	L.B.B.B.	R.B.B.B.	Infarct Q	ST-T	Long PR	L.V.H.	Total
QRS LOOPS							
I	3	3	1	2		1	10
II	1	6	2	5	2	2	18
III		4		1			5
	4	13	3	8	2	3	33
T LOOPS							
I	3	4	2	4		1	14
II	1	8		3	2	2	16
III		2	1				3
	4	14	3	7	2	3	33

reliability of uniform skin contact and the short-circuiting effect of the sponge. It is believed that this requires more study in a larger number of individuals. The multiple electrode is fairly simple to apply in the male, despite the 30 or more individual contact points. It is more expensive than the other systems because it requires 30 matched resistors and construction of a durable matrix assembly with internal wiring that will not break with repeated use. The Schmitt system is only slightly more complicated than the Frank system to apply. It has the great advantage of having been evaluated for a 5- by 5- by 5-cm. volume of dipole positions in homogeneous model studies and poses none of the problems presented by the other 3 systems in applying to the female.

A greater portion of our study was concentrated on the Z lead because this has been the most difficult one to devise from both the theoretical and practical standpoints, and has provided the source of greatest variability in earlier systems. Similarity of the loops recorded

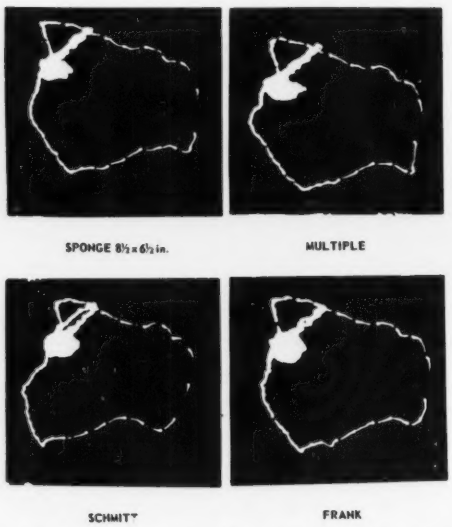

FIG. 5. Excellent matching obtained with the four X leads. The X lead goes from right to left. The Y lead, which is the same in each case, goes from top to bottom.

by all 4 systems suggests that this problem of an accurate Z lead has been solved for a majority of subjects. There are several theoretical explanations for the significant discrepancies that occurred in the 5 Z-lead studies in our series: 1. The heart may be representable by a single equivalent dipole, but its location may be outside the volume within which a given system is accurate. 2. The heart may be representable by a single equivalent dipole at any instant of time but its location may migrate outside the volume covered accurately by a given system. 3. The heart may be representable by a distribution of dipoles occupying a volume larger than that covered accurately by a given system. 4. The limits of accuracy for the systems covering a given region may allow a sufficient degree of latitude that dissimilar loops can still be accounted for. 5. There may be inhomogeneities in the conducting mediums of sufficient magnitude to affect the results. 6. Finally, a factor not encountered in our series, namely, gross distortion of the volume conductor by bizarre thoracic contour, such as pigeon breast, funnel chest, or marked kyphosis.

The results in our X-lead study were remarkably good in all the 22 subjects studied.

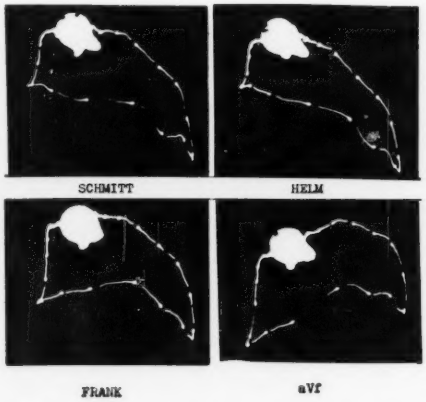

FIG. 6. Results obtained in matching the 4 Y leads, which go from top to bottom. The X lead, which is the same in each case, goes from right to left. The Schmitt, Frank, and Helm leads were very similar but aV_F was significantly at variance with the other 2 systems. This was repeated on 3 different days in this subject with the same results.

In the study of the Y lead we encountered 3 cases of 13 in which aV_F was significantly dissimilar to the Frank, Helm, and the Schmitt Y. This could be explained by the variability of the Wilson central terminal position in image space.

In some cases, while the QRS loops compared well, in the same subject the T loops were dissimilar and vice versa. This may also be explained on the theoretical grounds mentioned above.

The fact that loops derived from different systems were dissimilar in 5 individuals for the Z component does not necessarily indicate that any one of the methods is in error. Each system could be fundamentally sound based on what it was designed to do and still produce different loops because of reasons enumerated above. If all loops are the same, then the heart acts either as a single equivalent dipole or a number of dipoles within a 5- by 5- by 5-cm. volume. This is the limit of reasonable accuracy for the Schmitt and Frank systems, provided the latter is centered properly. It is possible that the multiple and sponge electrodes accurately cover a larger volume than the Schmitt system but this point has not been adequately studied in 3-dimensional models.

TABLE 3.—*Relative Size of Lead Vectors*

Lead	System	Length of lead	No. of cases	Per cent S.D.
Z	Schmitt	1.00*	47	
Z	Frank 5 I.C.S.	1.03	47	32.0
Z	Frank 4 I.C.S.	1.15	47	21.8
Z	Multiple	1.31	47	26.7
Z	Large sponge (Helm)	1.33	47	17.2
Z	Small sponge	1.41	47	23.4
X	Schmitt	1.33†	24	
X	Frank 4 I.C.S.	1.16	24	18.4
X	Multiple	1.17	24	14.8
X	Helm	1.09	10	
Y	Schmitt	1.40‡	10	
Y	Frank	.98	10	
Y	Helm	1.31	10	
Y	aVf	1.11	10	

* The Schmitt Z lead was arbitrarily assigned the value of unity. In all 3 components the Schmitt system, without the required external normalization, was used as a reference for the above table. For example, the ratio of the Frank Y to the Schmitt Y lead vector is given by .98 divided by 1.40.

† Requires external normalization factor of .75.

‡ Requires external normalization factor of .71.

Although Burger's contributions to vectorcardiography are of the greatest importance, his system was not used because it does not compensate for variable dipole locations.[10]

Our present study suggests that the 4 systems used were interchangeable judged by present clinical standards in all normal individuals and in a majority of the abnormal subjects. However, there was a significant difference among the 4 systems in at least 5 individuals. In 5 subjects with significant Z-lead differences among the systems the 2 electrodes of large area, namely, the sponge and multiple, resembled each other but differed considerably from the Schmitt and Frank, which in turn resembled each other. This raises a question as to which type of system is more accurate. The answer to this problem could be determined only by more fundamental studies or judged on an empirical basis of superior diagnostic accuracy and usefulness.

SUMMARY

The results of study of the Z leads in 60 subjects indicated that the systems were inter-

changeable in over 90 per cent of the cases for both QRS and T with regard to shape and orientation. Of the X lead studied in 24 subjects the systems were interchangeable for the QRS in all of the cases, and the T in 90 per cent. The evidence suggests that the Y lead is fundamentally a head-to-foot lead as recommended by Schmitt, with refinements introduced by Frank and Helm that produce little or no difference in the shape of the lead and only slight difference in amplitude.

Normalization data for the various systems was obtained, based upon comparison of wave forms.

Similarity of vectorcardiograms derived from 4 different systems in a large majority of subjects supports the validity of the individual methods of analysis. Theoretical possibilities for observed instances of dissimilarity are suggested.

In the recumbent position the Frank system at the fourth interspace gave better similarity with the other systems than when used at the fifth interspace. The Frank system seemed to be significantly influenced by the level at which the electrodes were placed in approximately 10 per cent of the subjects studied.

Results with the 2 electrodes of large area (sponge and multiple) were different from those obtained with the Frank and Schmitt systems in 5 subjects.

Summario in Interlingua

Le resultatos del studio del derivationes Z in 60 subjectos indicava que le systemas esseva mutualmente excambiabile in plus que 90 pro cento del casos quanto al configuration e al orientation de QRS e etiam de T. Le studio del derivationes X in 24 subjectos indicava excambiabilitate mutual del systemas quanto a QRS in omne casos e quanto a T in 90 pro cento. Le datos indica que le derivation Y es fundamentalmente un derivation capite-a-pede secundo le recommendation de Schmitt, con raffinamentos introducite per Frank e Helm que produce pauc o nulle differentia in le configuration del derivationes e solmente leve differentias in lor amplitude.

Datos de normalisation pro le varie systemas esseva obtenite super le base de comparationes del configuration del undas.

Le similaritate del vectocardiogrammas derivate ab quatro differente systemas in le grande majoritate del subjectos supporta le validitate del methodos individual de analyse. Es offerite possibile explicationes theoric del observate casos de non-similaritate.

In le position recumbente le systema Frank, usate al quarte interspatio, resultava in un melior similaritate con le altere systemas que le mesme systema usate al quinte interspatio. In circa 10 pro cento del subjectos studiate, le systema Frank pareva esser influentiate significativemente per le nivello a que le electrodos esseva placiate.

Le resultatos obtenite per medio del 2 electrodos de grande areas (typo a spongia e typo multiple) differeva in 5 subjectos ab le resultatos obtenite per le systemas Frank e Schmitt.

REFERENCES

1. Schmitt, O. H., and Simonson, E.: The present status of vectorcardiography. Arch. Int. Med. **96:** 574, 1955.
2. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography. Circulation **13:** 737, 1956.
3. McFee, R., and Johnston, F. D.: Electrocardiographic leads: III. Synthesis. Circulation **9:** 868, 1954.
4. Helm, R. A.: An accurate lead system for spatial vectorcardiography. Am. Heart J. **53:** 415, 1957.
5. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial vectorcardiography: Technique for the simultaneous recording of the frontal, sagittal, and horizontal projections. I. Am. Heart J. **41:** 483, 1951.
6. Schaffer, A. I., Bergmann, P. G., Boyd, L. J., Mirkinson, A., and Beinfield, W. H.: Eccentricity as a cause of the difference between the vectorcardiograms registered by the cube and tetrahedal systems. Am. Heart J. **45:** 448, 1953.
7. Gelfand, D., and Bellet, S.: Spatial vectorcardiography. J. Philadelphia General Hospital **4:** 135, 1953.
8. Pipberger, H. V., and Lilienfield, L. S.: Correlation of two corrected vectorcardiographic systems with the tetrahedron and cube system in humans. National Biophysics Conference, Columbus, Ohio, 1957.
9. Frank, E.: A direct experimental study of three systems of spatial vectorcardiography. Circulation **10:** 101, 1954.
10. Burger, H. C., and van Milaan, J. B.: Heart vector and leads. Brit. Heart J. **8:** 157, 1946; **9:** 154, 1947; **10:** 229, 1948.

Pulmonary Artery Stenosis

By Margaret B. Vermillion, M.D., Leonard Leight, M.D., and Lawrence A. Davis, M.D.

Although the number of cases of stenosis of a branch or branches of the pulmonary artery reported in the literature is small, this congenital lesion is being recognized with increasing frequency. This report is a description of 2 cases seen within 1 year. Both cases were studied by means of cardiac catheterization and angiocardiography. In both there were complicating congenital heart lesions.

SINCE the description by Möller[1] in 1953 of stenosis of peripheral pulmonary arteries, this congenital lesion has been recognized with increasing frequency. The lesion is of interest both from a clinical and physiologic standpoint. From the latter standpoint, there is sufficient documentation to warrant the inclusion of this congenital anomaly as one of the causes of right ventricular hypertension. From a clinical standpoint, pulmonary artery stenosis appears in some instances to be an additional cause of a continuous murmur heard over the thorax.

We have recently seen 2 cases studied both by cardiac catheterization and by selective angiocardiography that are examples of stenosis of a peripheral pulmonary artery. The first case is of interest in that a continuous murmur had been heard over this patient's thorax for some years. The second case is an example of stenosis of a peripheral pulmonary artery demonstrated both by cardiac catheterization and angiocardiography.

Case Reports

Case 1. A 10-year-old white girl was admitted to the hospital on July 9, 1956. She and her identical twin were the product of a 7 months' pregnancy. Each twin weighed 3 pounds at birth. The patient was not known to be cyanotic during her 2-month stay in the premature nursery, but on discharge from the hospital the mother was informed that the patient had a heart lesion. The patient gained weight slowly but was able to play, run, and ride a bicycle without difficulty. No cyanosis had ever been noted. At the time of admission, the patient weighed 10 pounds less and was 2 inches shorter than her twin, who had no known congenital anomaly. The remainder of the history was noncontributory.

Physical examination revealed a frail child appearing younger than the stated age of 10 years. There was a suggestion of cyanosis of the lips and nailbeds. Weight was 45 pounds, height 52 inches, respiration 16 per minute, cardiac rate 108 per minute, and blood pressure 110/80 mm. Hg in both arms. The positive physical findings were limited to the thorax. The point of maximum impulse was located 1.5 cm. to the left of the midclavicular line. No thrills were palpable. Regular sinus rhythm was present. A continuous murmur of grade II to III intensity was audible at the second right intercostal space, 4 cm. from the sternal border. The continuous murmur changed little in character throughout the cardiac cycle and was not modified by respiration or change in body position. A grade III, harsh, blowing, systolic murmur was heard along the left sternal border. The second sound at the pulmonic area was accentuated.

Red blood cell count was 4.6 million and the hemoglobin was 12.5 Gm. per 100 ml. Electrocardiogram revealed right ventricular hypertrophy. X-ray of the chest and cardiac fluoroscopy revealed a heart normal in size in its transverse diameter. There was marked prominence of the main pulmonary artery segment. The hilar shadows appeared accentuated and showed brisk pulsation. The peripheral pulmonary vascularity was interpreted as being within normal limits. The aorta descended on the left. The left atrium was not enlarged.

Cardiac catheterization was performed in the usual fashion on July 10, 1956, under rectal Avertin anesthesia. The findings are summarized in table 1. During catheterization, the catheter entered the aorta from the right ventricle. In addition, the catheter appeared to enter an anomalous pulmonary vein draining into the right atrium.

The data were interpreted as indicating the presence of a high interventricular septal defect with considerable pulmonary hypertension and possibly an anomalous pulmonary vein draining into the right atrium; however, no left-to-right shunt at the level of the atrium was demonstrated.

Immediately after pressure recordings and blood sampling were completed, the catheter was reinserted into the right ventricle. Twenty-two milliliters of 70 per cent sodium acetrizoate (Urokon)

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Dr. Vermillion is a Public Health Service Research Fellow of the National Heart Institute (1956–1957).

TABLE 1.—*Case 1, Cardiac Catherization Data*

Pressures in mm. Hg
- pulmonary artery: 102/59 (80)
- right ventricle: 115/4/7
- right atrium, mean: 2
- aorta: 100/61 (84)

Blood oxygen content, volume per cent
- inferior vena cava: 13.91
- superior vena cava: 12.76
- right atrium, near superior vena cava: 13.21
- right atrium, mid: 13.19
- right ventricle, mid: 13.88
- pulmonary artery, left: 14.87
- aorta: 17.64
- blood oxygen capacity: 19.22
- arterial oxygen saturation: 91.78%

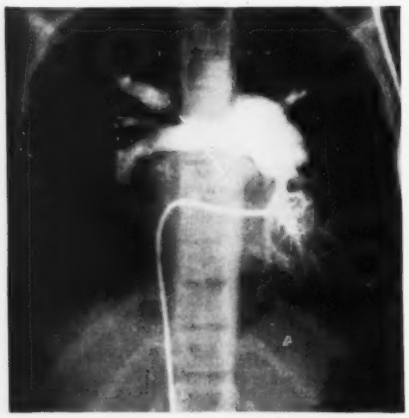

FIG. 1. Case 1. Angiocardiogram demonstrating stenosis of a branch of the pulmonary artery with poststenotic dilatation. Catheter in right ventricle.

were injected under pressure through the catheter with film exposure beginning automatically at the time of injection. By means of an Elema bi-plane angiocardiogram x-ray apparatus,* 6 films per second were obtained simultaneously in the antero-posterior and lateral positions for a total of 4 seconds. The opaque material was seen entering the right ventricle and passing through a high septal defect into the left ventricle and then into the aorta. The aorta appeared to be normally located with no overriding of the interventricular septum. The main pulmonary arteries appeared enlarged. An unusual stenosis of one of the superior branches of the right pulmonary artery with a poststenotic dilatation was seen (fig. 1). No other areas of narrowing of the

* Manufactured by Elema, Industrivägen 23, Stockholm, Solna Sweden.

TABLE 2.—*Case 2, Cardiac Catheterization Data*

Pressures in mm. Hg
- pulmonary artery, right peripheral branch: 20/8
- pulmonary artery, main: 36/8
- right ventricle: 59/2/6
- right atrium, mean: 2

Blood oxygen content, volume per cent
- inferior vena cava: 7.84
- superior vena cava: 8.54
- right atrium, near superior vena cava: 9.42
- right atrium, mid: 9.46
- right ventricle, near tricuspid valve: 9.42
- right ventricle, mid: 10.21
- right ventricle, near pulmonic valve: 9.46
- pulmonary artery, right: 9.63
- pulmonary artery, main: 9.59
- pulmonary vein, right: 12.48
- femoral artery: 11.12
- blood oxygen capacity: 12.59
- arterial oxygen saturation: 86.68%

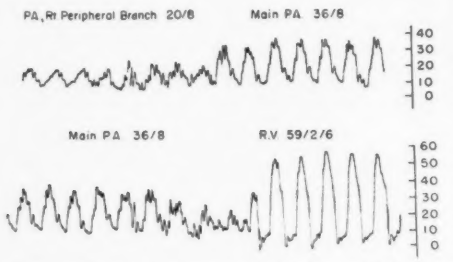

FIG. 2. Case 2. Pressures obtained on withdrawing catheter from peripheral branch of right pulmonary artery to right ventricle.

pulmonary vasculature were demonstrated. The dye returned normally to a moderately enlarged left atrium.

Case 2. A 19-month-old white boy was admitted to the hospital on March 23, 1957. He was the product of a 7 months' pregnancy and weighed 3 pounds, 6 ounces at birth. The presence of a heart lesion was noted soon after birth. The patient failed to gain weight normally and tired easily while playing. No cyanosis had been noted by the parents.

Physical examination revealed a small baby, who weighed 17¾ pounds and was 32 inches tall. Respirations were 28 per minute, cardiac rate was 88 per minute, and blood pressure was 95/65 mm. Hg The positive physical findings were limited to the thorax. The point of maximal impulse was in the fifth intercostal space at the midclavicular line. A grade III to IV harsh, blowing, systolic murmur was audible over the entire precordium but was loudest at the second to fourth intercostal space to the left of the sternum, and a thrill was palpable here. The second pulmonary sound was grossly

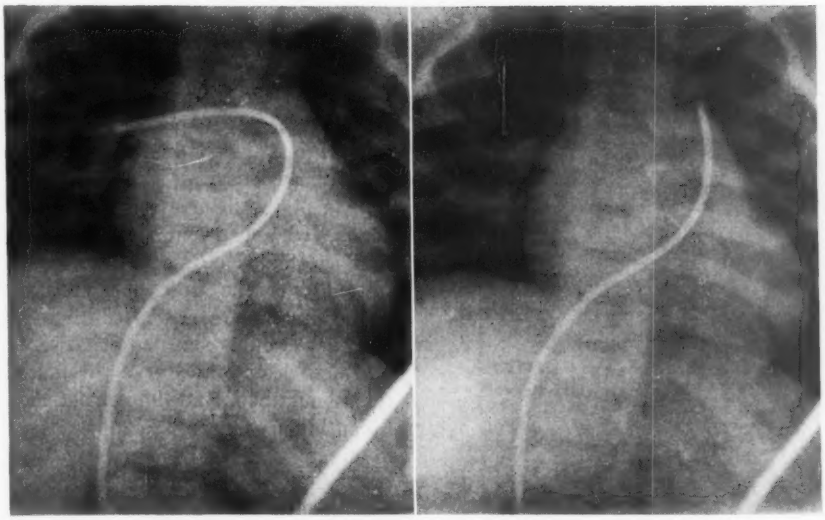

FIG. 3. *Left.* Case 2. Location of catheter when pressure obtained labeled pulmonary artery, right peripheral branch.

FIG. 4. *Right.* Case 2. Location of catheter when pressure obtained labeled main pulmonary artery.

diminished. There was no cyanosis and the rhythm was regular. X-ray of the chest revealed an enlarged heart with no unusual or diagnostic configuration. The lung fields showed questionable overvascularization. The fluoroscopist reported enlargement of the left atrium.

The red blood cell count was 4 million, and the hemoglobin was 12.9 Gm. per 100 ml. The electrocardiogram revealed right ventricular hypertrophy.

Cardiac catheterization was performed in the usual fashion on March 25, 1957, under thiopental (Pentothal) and meperidine (Demerol) anesthesia The findings are summarized in table 2. During catheterization the catheter entered a pulmonary vein on 2 occasions apparently from the right atrium; however, as in the previous case, our failure to demonstrate a left-to-right shunt at the level of the atrium casts doubt as to whether anomalous pulmonary venous drainage was truly present. The catheter was inserted into the right ventricle and then into a pulmonary artery, finally entering a peripheral branch of the right pulmonary artery. The pressures obtained in pulling back from the peripheral branch of the right pulmonary artery to the right ventricle just proximal to the pulmonary valve are illustrated in figure 2.

The location of the catheter at the time pressures were obtained from a peripheral branch of the right pulmonary artery and the main pulmonary artery is illustrated in figures 3 and 4 respectively. The pressure in a peripheral branch of the right pulmonary artery was 20/8 mm. Hg (figs. 2 and 3). As the catheter was pulled out to the main pulmonary artery, there was a sudden rise in pressure to 36/8 mm. Hg (figs. 2 and 4). When the catheter was then pulled back to the right ventricle, there was a further rise in systolic pressure that appeared to begin sharply at the pulmonary valve, the right ventricular pressure just proximal to the valve being 58/2/6 (fig. 2). There was no further rise in right ventricular pressure in other areas of the right ventricle. These pressure relationships were demonstrated several times.

The data were interpreted as indicating both a stenosis of a peripheral branch of the pulmonary artery and a valvular pulmonic stenosis. A mild pulmonary hypertension was present proximal to the peripheral pulmonary stenosis. In addition, the possibility of an anomalous pulmonary vein draining into the right atrium could not be excluded.

Immediately after pressure recordings and blood sampling were completed, the catheter was again placed in the right ventricle. Ten milliliters of 70 per cent sodium acetrizoate (Urokon) were injected under pressure through the catheter with film exposure beginning automatically at the time of injection. Again by means of the Elema bi-plane angiocardiogram apparatus, 6 films per second were obtained simultaneously in the antero-posterior and lateral projections for a total of 4 seconds. Soon after injection of the dye, the catheter whipped from the right ventricle into the right atrium and most of the dye was injected into the right atrium. A representative film of the angiocardiographic study is illustrated in figure 5. No right-to-left shunt was demonstrated at angiocardiography. A constriction

FIG. 5. Case 2. Angiocardiogram demonstrating stenosis of right pulmonary artery. Catheter has whipped into right atrium from right ventricle.

of the right main pulmonary artery just distal to the bifurcation can be seen.

DISCUSSION

Stenosis of peripheral branches of the pulmonary artery was first described by Möller in 1953.[1] This author presented a patient with a continuous murmur over the aortic area, electrocardiographic evidence of right ventricular hypertrophy, and cardiac enlargement with prominence of the pulmonary conus on roentgenographic examination. Cardiac catheterization revealed only hypertension of the pulmonary artery and of the right ventricle. Arterial oxygen saturation was normal. Selective angiocardiography of the pulmonary artery showed multiple constrictions with poststenotic dilatations. In 1955 Powell and Hiller[2] described a 5-year-old patient with a history of tiredness, failure to gain weight, and dyspnea on exertion. A continuous murmur was heard over the pulmonic area. On angiocardiography a narrowing of both the right and left pulmonary arteries immediately distal to the bifurcation of the main pulmonary artery was found. Dilatation of the main pulmonary artery proximal to the narrowing was seen. Of the 4 cases of peripheral pulmonary stenosis and associated pulmonary hypertension reported in 1955 by Arvidsson and associates,[3] 1 patient had a continuous murmur, which was heard over the entire chest. A selective angiocardiogram of the pulmonary artery of this patient revealed a dilated pulmonary artery with marked narrowing of short areas of the lumina of the lobar arteries. The other 3 patients, who had similar angiocardiographic findings, had a coarse murmur widely transmitted over the back and precordium that was audible, however, only during systole.

Thus it would seem that stenosis of a peripheral branch or branches of the pulmonary artery should be included as one of the causes of a continuous murmur heard over the precordium and we believe our case 1 is another example of the association of this defect and the accompanying murmur. In this case, the stenosis of the pulmonary artery played a questionable part in the pulmonary hemodynamics in view of the demonstration of a high interventricular septal defect.

Since the original description of stenosis of branches of the pulmonary artery, several other reports in addition to those enumerated above have appeared. In 1953, Schumacher and Lurie[4] referred to a 14-year-old patient with cyanosis, clubbing, physical incapacity, and lethargy. At thoracotomy, the main pulmonary artery was described as approximately normal in size or a little smaller than normal. About 2 cm. distal to its origin at approximately the region of the bifurcation, the artery became very small and a calcified stenotic lesion was found in this area.

Sondergaard[5] in 1954, reported 3 cases of peripheral pulmonary stenosis. All of these patients had associated lesions, 2 suggestive of tetralogy of Fallot and 1 of an atrial septal defect.

Gyllenswörd and co-workers[6] have recently reported 8 cases of the anomaly under discussion, in 1 of which the presence of a stenosis of a peripheral branch of the pulmonary artery was demonstrated at the time of cardiac catheterization by means of pull-out pressures. Coles and Walker[7] have also described a case in which pull-out curves demonstrated the presence of pulmonary artery stenosis. We believe

our second case is another example of this lesion demonstrated at the time of catheterization. Our case apparently has an associated valvular pulmonic stenosis. There appears to be a mild pulmonary hypertension present proximal to the stenotic pulmonary artery.

Whether or not significant right ventricular hypertension will result from stenosis of the pulmonary artery undoubtedly depends on the degree and location of the stenosis and the number of branches involved. Although we are unaware of the description of this lesion in adults, there appears to be no reason why in some cases this abnormality should not be compatible with a relatively long life span. From the small number of cases thus far reported, it is apparent that many of the cases of stenosis of the peripheral pulmonary artery have other congenital cardiac defects. This was so in both of our cases.

Summary

Two examples of stenosis of a branch of the pulmonary artery are presented. Both patients were studied by means of cardiac catheterization and angiocardiography. One case presented with a continuous precordial murmur and the presence of the stenosis and poststenotic dilatation was demonstrated by means of angiocardiography. The second case is another report of the demonstration at the time of cardiac catheterization of stenosis of the pulmonary artery. Both patients had associated cardiac anomalies, the first case a high interventricular septal defect and the second case a valvular pulmonic stenosis.

Summario in Interlingua

Es presentate duo exemplos de stenose de un branca del arteria pulmonar. Ambe le patientes esseva studiate per medio de catheterisation cardiac e angiocardiographia. Le prime veniva al consulta con un continue murmure precordial, e le presentia del stenose e de dilatation poststenotic esseva demonstrate per medios angiocardiographic. Le secunde representa un exemplo additional del demonstration de stenose del arteria pulmonar al tempore de catheterisation cardiac. Ambe le patientes habeva associate anormalitates cardiac: le prime un defecto del septo alto-interventricular, le secunde un stenose del valvula pulmonar.

REFERENCES

1. Möller, T.: A case of peripheral pulmonary stenosis. Acta paediat. **42:** 390, 1953.
2. Powell, M. L., and Hiller, H. G.: Pulmonary coarctation. M. J. Australia **1:** 272, 1955.
3. Arvidsson, H., Karnell, J., and Möller, T.: Multiple stenosis of pulmonary arteries associated with pulmonary hypertension, diagnosed by selective angiocardiography. Acta radiol. **44:** 209, 1955.
4. Schumacher, H. B. J., and Lurie, P. R.: Pulmonary valvulotomy-description of a new operative approach with comments about the diagnostic characteristics of pulmonic valvular stenosis. J. Thoracic Surg. **25:** 173, 1953.
5. Sondergaard, T.: Coarctation of the pulmonary artery. Danish Med. Bull. **1:** 46, 1954.
6. Gyllenswörd, A., Lodin, H., Lundberg, A., and Möller, T.: Congenital multiple peripheral stenoses of the pulmonary artery. Pediatrics **19:** 399, 1957.
7. Coles, J. E., and Walker, W. J.: Coarctation of the pulmonary artery. Am. Heart J. **52:** 469, 1956.

Cerebral symptoms, of a remarkable character, are commonly present in this disease. These consist in the occurrence of repeated pseudo-apoplectic attacks, of various degrees of intensity and duration. They are seldom followed by paralysis. Attacks of vertigo, dimness of vision, and syncope, are observed.—William Stokes. *The Diseases of the Heart and the Aorta.* Dublin, 1854.

Massive Occlusion of the Main Pulmonary Artery and Primary Branches

Case Report

By JORMA M. LEINASSAR, M.D., AND NELSON R. NILES, M.D.

This case of massive thrombotic occlusion of the main pulmonary artery is reported because of the size, extent, and duration of the process, because of the prominent findings leading to the correct clinical diagnosis, and, finally, because of the interesting secondary pathologic changes including myocardial infarction without significant coronary arteriosclerosis or occlusion.

MASSIVE occlusion of the main pulmonary artery and its primary branches is believed seldom compatible with prolonged survival. However, a number of reports exist indicating a duration of from several months to several years. No documented cases were found to compare, either in length of life after the episode or in degree of pulmonary artery occlusion, with our patient who survived about 6 years. Chronic obstruction of the major pulmonary arteries with cor pulmonale has been reported as a clinical syndrome more frequently in recent years.[1-4] The cause of pulmonary embolism seems directly related to peripheral vascular disease, namely, phlebothrombosis or possibly thrombophlebitis. Emboli are considered to be uncommon as a result of thrombophlebitis, but a red, swollen, tender extremity may represent phlebothrombosis rather than phlebitis, thus causing a misleading opinion regarding the origin of emboli and erroneously raising the frequency of embolism reported as due to thrombophlebitis. The total number of reported cases of long-standing pulmonary embolism may be less than 200 and the majority of these has been discovered at autopsy. No reports were found in which an antemortem diagnosis was made before 1940.

This report is intended to call attention to 2 important phases of this condition. First the duration of life after the initial episode (1950) or following ones (1951), (at least 4 and possibly 6) and second, the recognition of long-standing thromboembolic occlusions of major pulmonary arteries.

Patients surviving the acute shock of large pulmonary emboli will benefit from present-day cardiovascular surgical procedures and medical therapy. Severe pulmonary hypertension and its concomitant right heart failure may be prevented or altered. The procedures of embolectomy, endarterectomy, and artery resection will have their place for certain patients. Indeed, one report is available from France of a cure by resection of the involved segment of pulmonary artery.[5] The use of anticoagulant drugs is restricted to the prevention of the primary thrombosis; they cannot dissolve thrombi or emboli. However, they may reduce embolization by inhibition of further clotting.[6]

It is important to emphasize that patients may survive after severe embolization for a prolonged period as shown by the case to be presented. The long duration of symptoms is not at all incompatible with a clinical diagnosis, which should be suspected, particularly in younger patients, with bizarre symptoms related to pulmonary and cardiovascular systems. In part, some of the reasons for infrequent or belated diagnosis may be due to adherence to too rigid criteria, with classical symptoms and signs developing only in the late phases of pulmonary hypertension.[7, 8] Cardiac catheterization and angiocardiography are useful special diagnostic procedures, but the diagnosis of obstruction of the major pulmonary arteries should be suspected or estab-

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hed on firm clinical grounds prior to the use these procedures.

Symptoms and signs of pulmonary embolism include shock, syncope, weakness, cough, yspnea, sweating, chest pain, and cardiac rhythmia; later, cyanosis, hemoptysis, clubing of digits (if arterial oxygen saturation is hronically less than 70 to 88 per cent), and oarseness may be seen. Right heart dilatation cor pulmonale) and failure occur secondary o pulmonary hypertension. X-ray studies ay reveal a hilar mass or prominent vascular atterns and clear pulmonary fields; or cardiac nlargement may be present. The left hilar shadow consists of the main pulmonary artery and proximal portion of the left main branch, so that if these are occluded, fluoroscopy will not show hilar and peripheral vascular hyperactivity or "dance."[9] Murmurs are not characteristic and may be due to turbulence in the pulmonary artery from the clot. Electrocardiographic evidence of right ventricular hypertrophy or strain often indicates a pulmonary artery pressure greater than 30 mm. Hg and signifies far advanced disease.[10, 11]

The anatomic components of pulmonary hypertension include thrombi of varying stages and vascular intimal and medial thickening; possibly neurogenic constriction of pulmonary vessels is a physiologic component.

Pathology

Pathologic changes resulting from long-standing massive thrombotic occlusions of pulmonary arteries usually include hypertrophy and dilatation of the right side of the heart. The degree of organization and recanalization of the thrombotic emboli is dependent upon time and the sizes of the vessel involved and of the clot itself; many thrombi of long standing in larger vessels show almost complete lack of organization and are only a densely hyalinized mass. Arteriosclerosis of major and minor pulmonary arteries seems to result mainly from the incorporation of thrombi in the vessel wall. All degrees of change can be seen in the lung itself from a completely normal microscopic picture through minor changes as a result of old infarction, to grossly and microscopically obvious healed infarcts. Secondary inflammatory processes, of course, are frequent.[12, 13]

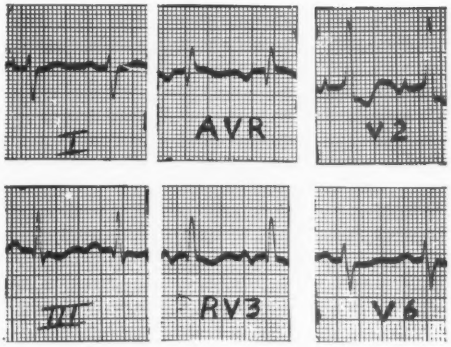

Fig. 1. Right axis deviation with right ventricular hypertrophy and incomplete right bundle-branch block evidenced by large R wave in RV_3 and V_2 exceeding 7 mm. and large R wave in aV_R.

Case Report

L. J., a 40-year-old white man was first seen early in 1955, complaining of shortness of breath, palpitations, loss of strength, and loss of 15 pounds in weight; examination revealed cyanosis, early clubbing of fingers and toes, hypotension (100/70), cardiac enlargement, pulmonary congestion, polycythemia, a cold left leg, and a superficial "thrombophlebitis" of the right calf. There was a grade II, apical, systolic murmur and the pulmonic second sound was duplicated. Lower sternal dullness was noted. The electrocardiogram indicated right ventricular hypertrophy and incomplete right bundle-branch block (fig. 1).

He gave a history of varicosities of both legs and "phlebitis," (undocumented as to thrombophlebitis) beginning in 1943, and resulting in a varicose ulcer on the left leg by 1946, for which a left superficial saphenous ligation was done in 1947. In early 1950, he suffered sudden chest pain and hemoptysis and later had 5 or 6 similar attacks in 1951. At this time he was given digitalis because of extrasystoles. In October 1954, recurrent ulcers of the left leg were treated by stripping of an upper leg vein. The cardiopulmonary disease and syndrome of pulmonary artery obstruction remained undetected although a chest x-ray as early as 1951 had revealed pulmonary densities and prominent hilar shadows (fig. 2). Blood pressure varied between 80/50 and 100/70. Prior to death in March 1956, the hemoglobin was 18.2 Gm. per 100 ml. and the hematocrit value was 59.

Autopsy Findings. The main pathologic finding was a single, huge, old, thrombotic pulmonary embolus involving the main pulmonary artery and

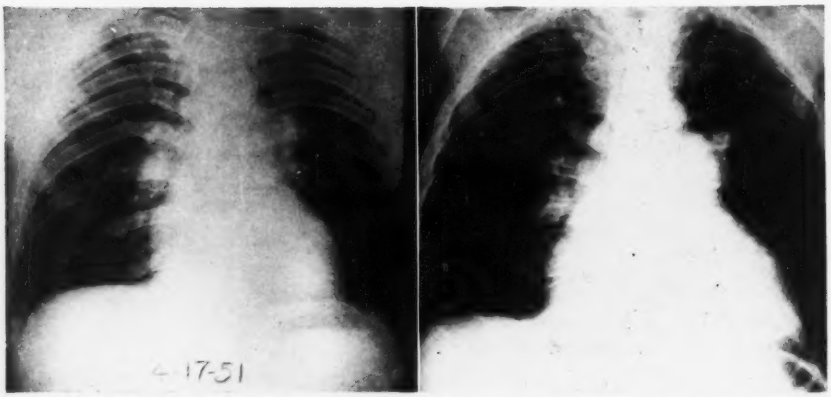

FIG. 2. Progressive cardiac enlargement, hilar prominence, and clear lung fields, beginning in 1951, to pulmonary nodularity in 1956.

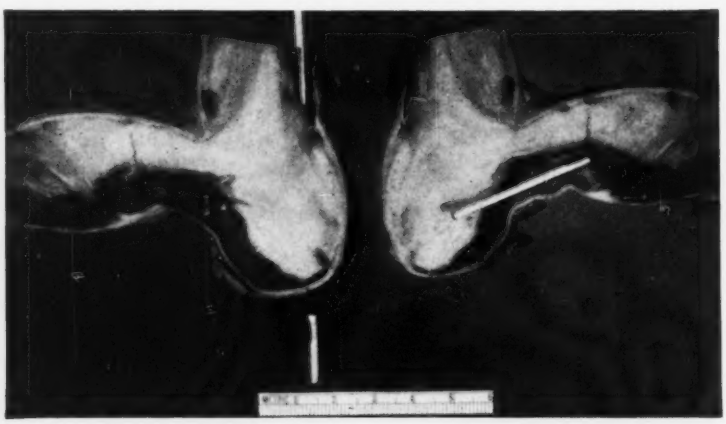

FIG. 3. Longitudinal section of extrapulmonary portions of main pulmonary artery and right and left branches; the main artery is below; the longer limb is the right branch and it shows more recent thrombosis. The wooden probes indicate the remaining channels to the right and left sides.

its major branches bilaterally (fig. 3); the proximal end was just 1 cm. above the pulmonic valve ring. This artery and its branches were longitudinally sectioned and were estimated to be, in any single cross-sectioned area, at least 90 per cent filled with thrombus, which was old and laminated for the most part, pale, and firm (fig. 4). At a few points, especially in the distal segment of the right main arterial branch, there were softening, friability, and roughening, suggesting that some portions here may have been more recent. When this mass was followed out into the pulmonary arterial branches on both sides, numerous and irregular extensions into the smaller branches were revealed. A very tortuous channel around the thrombus existed from the proximal portion of the pulmonary artery into the periphery of both lungs. In the more peripheral portions of the arterial tree numerous other thrombotic masses were apparent. Some of these were organized and at least 1, measuring 6 mm. in diameter and progressing for a distance of approximately 2 cm., was not connected with the main thrombus.

There were marked right ventricular and right atrial hypertrophy and dilatation (fig. 5). The heart itself weighed, after fixation, 635 Gm. and measured 12.5 cm. in maximum transverse diameter.

There were 2 old, well healed myocardial infarcts and widespread myocardial fibrosis, without demonstrable coronary artery disease. One of these infarcts in the inferior portion of the interventricular septum extended to involve the right ventricular endocardium. Chronic progressive mural thrombosis of the right ventricle overlay this infarct. Another old thrombus was present in the right atrial appendage.

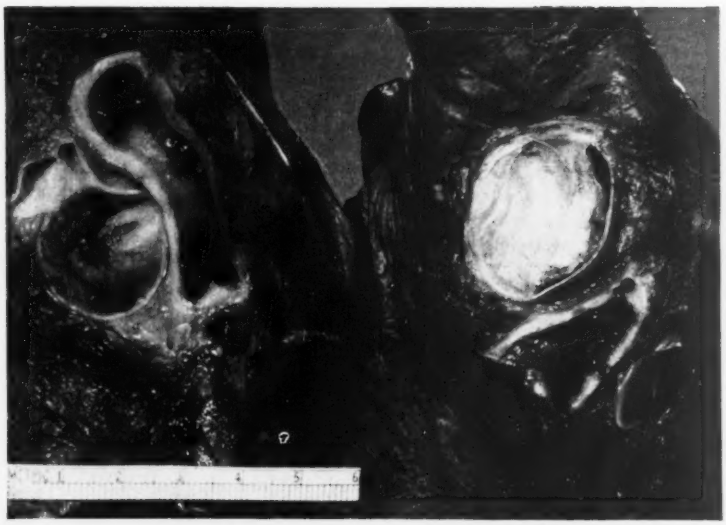

FIG. 4. Cross sections of right and left pulmonary arteries at entrances into lungs.

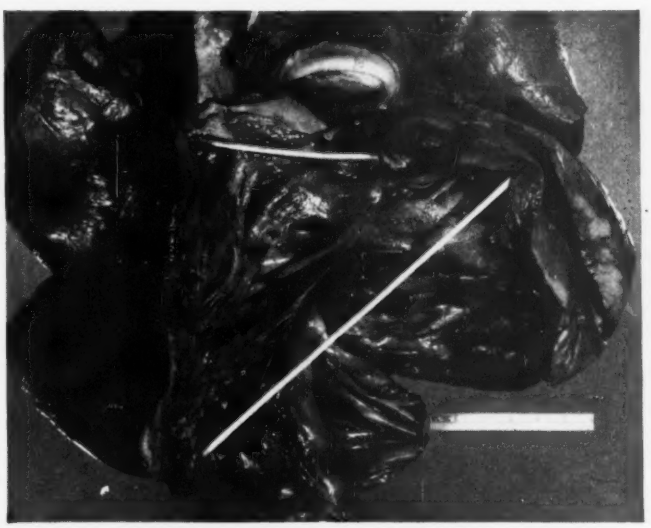

FIG. 5. Opened right ventricle with thrombotic mass presenting just above the pulmonic valve ring; marked ventricular dilatation; mural thrombosis in apex of ventricle seen on the lower right of photograph.

The coronary arteries were thin-walled and elastic, showing no arteriosclerosis. The pulmonic valve ring measured 9.3 cm. in circumference; other valve measurements were normal and there was no other significant valvular distortion. There were chronic focal degenerative pulmonary changes, possibly representing old, healed, patchy pulmonary infarcts. Chronic passive congestion of the liver was observed. An acute suppurative bronchitis with minimal focal bronchopneumonia was also present.

DISCUSSION

Clinicopathologic Correlation. Apparently this man suffered a tremendous pulmonary embolism in 1950, 6 years before death, and the

majority if not all of the disease resulted from this. There were other similar clinical episodes in 1951, probably as a result of smaller emboli breaking off from the major mass in the pulmonary artery, or possibly as a result of additional thrombosis being superimposed upon the original embolus, as suggested by the lamination. Obstruction of the pulmonary arterial system remained undetected through 1954. When seen early in 1955, he had definite evidence of severe chronic cor pulmonale by physical examination, x-ray, and electrocardiographic study.

The 2 old myocardial infarcts and focal myocardial fibrosis cannot be explained as the result of coronary artery disease; we think these have resulted from anoxemia due to pulmonary vascular obstruction. The right ventricular thrombosis was thought to be secondary to the myocardial infarction; it is rare for thrombosis to occur in the right ventricle from any cause, and therefore its occurrence here is probably connected with cor pulmonale. The thrombus in the right atrial appendage is readily explicable by right heart failure, as is the congestion of the liver.

Summary

A case of thrombotic pulmonary embolism is reported. This is apparently the most massive pulmonary artery obstruction of any significant duration in the literature; the length of life after the initial episode (6 years) is therefore especially surprising and also the longest yet reported.

A plea is made for proper etiologic diagnosis of cor pulmonale as well as for recognition of the syndrome of chronic pulmonary vascular obstruction.

Summario in Interlingua

Es reportate un caso de thrombotic embolismo pulmonar. Isto es apparentemente le plus massive obstruction pulmono-arterial de duration significative in le litteratura. Le superviventia durante 6 annos post le episodio initial es specialmente surprendente. Illo es le plus longe unquam reportate.

Es signalate le urgente necessitate del correcte diagnose etiologic de corde pulmonal e del recognition del syndrome de chronic obstruction pulmono-vascular.

References

[1] Hollister, L. E. and Cull, V. L.: The syndrome of chronic thrombosis of the major pulmonary arteries. Am. J. Med. **21:** 312, 1956.

[2] Ring, A., and Bakke, J. R.: Chronic massive pulmonary artery thrombosis. Ann. Int. Med. **43:** 781, 1955.

[3] Owen, W. R., Thomas, W. A., Castleman, B., and Bland, E. F.: Unrecognized emboli to the lungs with subsequent cor pulmonale. New England J. Med. **249:** 919, 1953.

[4] Ball, K. P., Goodwin, J. F., and Harrison, C. V.: Massive thrombotic occlusion of the large pulmonary arteries. Circulation **5:** 766, 1956.

[5] Boucher, H., Protar, M., and Bertein, J.: Anevrisme de la branche droite de l'artere pulmonaire par embol latent postphlebitique. J. franc. med. et chir. thorac **5:** 421, 1951.

[6] Harvey, R. M., Ferrer, I., and Cournand, A.: The treatment of chronic cor pulmonale. Circulation **7:** 932, 1953.

[7] Cournand, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary disease. Circulation **2:** 641, 1950.

[8] Heath, D., and Whitaker, W.: Hypertensive pulmonary vascular disease. Circulation **14:** 323, 1956.

[9] Healey, R. F., Dow, J. W., Sosman, M. C., and Dexter, L.: The relationship of the roentgenographic appearance of the pulmonary artery to pulmonary hemodynamics. Am. J. Roentgenol. **62:** 777, 1949.

[10] Cutler, J. G., Nadas, A. S., Goodale, W. T., Hickler, R. B., and Rudolph, A. M.: Pulmonary arterial hypertension with markedly increased pulmonary resistance. Am. J. Med. **17:** 485, 1954.

[11] Scott, R. C., Kaplan, S., Fowler, N. O., Helm, R. A., Westcott, R. N., Walker, I. C., and Stiles, W. J.: The electrocardiographic pattern of right ventricular hypertrophy in chronic cor pulmonale. Circulation **11:** 927, 1955.

[12] Barnard, P. J.: Pulmonary arteriosclerosis and cor pulmonale due to recurrent thromboembolism. Circulation **10:** 343, 1954.

[13] Marshall, E. W.: Cor pulmonale. Med. Clin. North America **38:** 1675, 1954.

The Emphysema Response to Forced Straining (Valsalva's Maneuver)

By HAROLD MILLS, M.D., AND ALBERT A. KATTUS, JR., M.D.

Changes in arterial pressure were recorded during and after forced straining (Valsalva's maneuver) in 29 patients with emphysema. The response in these patients differed greatly from that found in normal subjects and in patients with cardiac disease. Additional physiologic data did not serve to define the mechanisms of this unique response in emphysema to forced straining.

RECENTLY there has been a renewed interest in the physiologic effects of forced straining (Valsalva's maneuver). Particular emphasis has been placed on the blood pressure changes during and immediately after forced straining in an attempt to define more accurately the diagnosis of certain circulatory abnormalities, particularly hemodynamically significant mitral stenosis and the presence of congestive failure.[1-7] Little attention has been given to the manner in which pulmonary disease modifies the response to straining. The purpose of this paper is to present data obtained from observing circulatory changes during and immediately after Valsalva's maneuver in patients with pulmonary emphysema and to contrast these changes with responses in patients with normal and diseased hearts. The "emphysema response" is unique and to our knowledge has not been described except in our recent preliminary report.[8]

HISTORIC BACKGROUND

In an excellent historical review Dawson[9] summarized the early studies on the use of forced straining for investigation of various cardiovascular problems. Valsalva (1666–1723) is credited with the earliest description of the effect of forced straining on the circulation. In 1850, Weber described the effect of "chest compression" and noted syncope and convulsions after a particularly vigorous effort on his part. Approximately 35 years ago, Flack and Burton[10] utilized the Valsalva test for appraising physical fitness in Royal Air Force officers. In 1936, Hamilton and co-workers[11] divided the response to forced straining into 4 phases, a division subsequently utilized by others[2] in the diagnosis of "dynamically significant" mitral stenosis: (*I*) During the initial straining period a rise in the systolic and diastolic blood pressures; (*II*) as straining continues a gradual fall in systolic, diastolic, and pulse pressures; (*III*) immediately after cessation of straining a marked drop in systolic and diastolic pressures; (*IV*) within a few beats an increase in systolic and diastolic pressures to greater than control levels immediately followed by bradycardia.

Particular attention has been given to the pressure overshoot and bradycardia occurring in phase *IV*. Numerous studies have pointed out that an intact autonomic nervous system is needed for the overshoot and bradycardia, for if autonomic function is abolished by organic disease or drugs, these responses do not occur.[4, 5, 12-14] The overshoot has been attributed to blood entering a constricted arterial system after having been dammed back on the venous side.[18] McIntosh and co-workers[5] thought that the response is secondary to the interplay of cardiac output, total peripheral vascular resistance, and other poorly understood mechanisms. The bradycardia will never occur without the systolic overshoot, but a marked overshoot without significant bradycardia may occur. Bjork and associates[15] recorded a fall in left atrial pressure during straining. However, Yu and co-workers[7] noted that pulmonary capillary and pulmonary arterial pressures rose considerably at the onset of straining and then were maintained at approximately twice the

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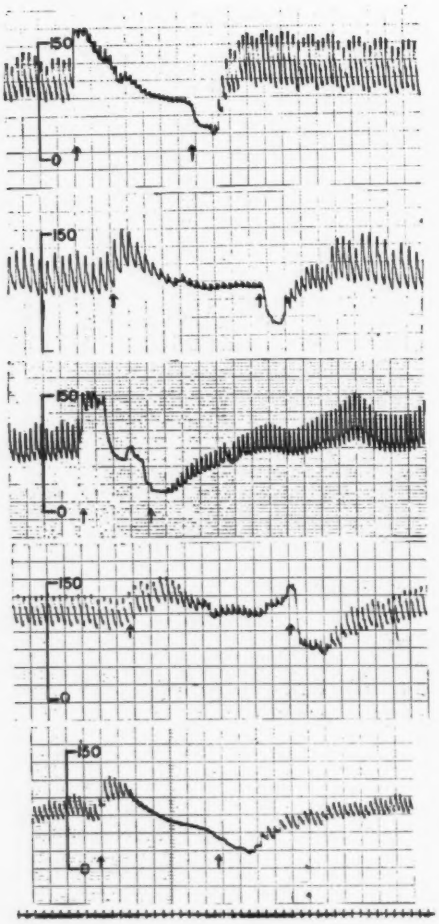

FIG. 1. Brachial arterial pulse tracings in 5 patients with emphysema. Forced straining occurred between arrows. Marked obliteration of pulse pressure is seen in all cases and delayed recovery is present in all but the top record. In the middle case the straining was terminated by a mild convulsion. Time marker is in seconds.

control value. In general, the pulmonary artery pressure rose to a greater extent than the pulmonary capillary pressure with no differences discernible between subjects with normal or high pulmonary capillary pressures. Lee and associates[16] have demonstrated that the effect of Valsalva's maneuver upon pulmonary artery pressure may be accounted for by the increased intrathoracic pressure during straining and by the post-straining increase in cardiac output.

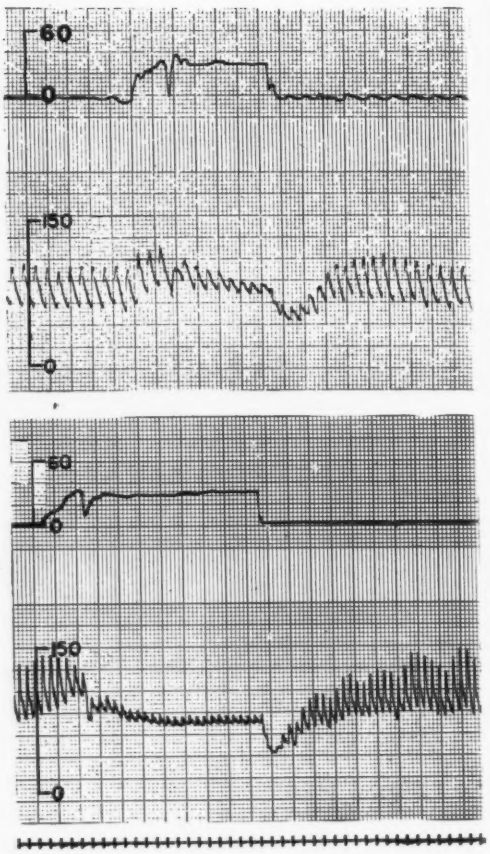

FIG. 2. Brachial arterial pressures (below) and intraoral pressures (above) in 2 cases of emphysema subjected to forced straining. Time marker is in seconds.

The duration of straining is not important provided it exceeds 7 seconds with an intrathoracic pressure of 30 mm. Hg or greater.[5] Intraoral pressure may give a falsely high measure of intrapleural pressure due to the tension of the distended cheeks.[17]

Elisberg's group[1, 2] have utilized the absence of a systolic overshoot and bradycardia in phase *IV* as a test for "dynamically significant" mitral stenosis although the validity of this method has been questioned.[5, 18] Greene and Bunnell[4] have emphasized that patients with mitral stenosis maintain their systolic pressures throughout the period of straining. They

TABLE 1.—*The Effect of Forced Straining*

	No. of cases	Terminal straining pulse pressure (mm. Hg) Mean	S.D.	Terminal straining PP* / Control pulse pressure × 100 Mean	S.D.	Time required for post-straining systolic pressure to return to control level (sec.) Mean	S.D.
Normal	9	21.2 ±	8.4	64.8 ±	38.4	4.80 ±	0.8
Emphysema	29	10.2 ±	8.9	24.0 ±	17.8	11.50 ±	4.4
Miscellaneous cardiac	80	39.0 ±	23.8	80.7 ±	52.4	6.9 ±	3.2

* pp = pulse pressure.

attributed this phenomonon to the large reservoir of blood in the left atrium of these patients and were unable to abolish this response with tetraethyl ammonium chloride. Sharpey-Schafer[6, 19] and Knowles and co-workers[3] have utilized the Valsalva maneuver for detecting pulmonary congestion of varying etiology. They noted that persons with left heart failure and pulmonary congestion maintain a persistently elevated arterial pressure during straining and have no post-straining overshoot or bradycardia. This failure was attributed to an elevated right ventricular diastolic pressure and peripheral venous pressure that prevented the usual obstruction of venous return caused by forced straining in normal subjects.[18, 20] Recently the observations of Sharpey-Schafer and Knowles and associates have been confirmed, although false negative and false positive responses were noted.[21]

METHODS

All subjects were studied while supine and fasting. The majority were given a mild sedative prior to the procedures. All of the normal subjects and those with emphysema were adult males. The miscellaneous cardiac group included 78 adult males and 2 adult females. A no.-17 needle was placed within the brachial artery and after good pulsatile flow was established, a stiff 24-inch (3 mm. internal diameter) polyethylene tube was attached to the needle and to a Statham pressure transducer. The arterial pressures were recorded on a Sanborn Twin-Viso direct-writing recorder. Each subject was directed to blow into a mouthpiece attached to a mercury manometer for visual recording of straining pressure. In most cases the manometer was also connected through a strain gage to the Sanborn apparatus in order to record the pressure and duration of straining. All subjects maintained forced straining for at least 10 seconds at a pressure of 30 to 40 mm. Hg. The terminal straining systolic and diastolic blood pressures were measured for the cardiac cycles immediately prior to the cessation of straining. In most subjects spirometric measurements were made in conjunction with these procedures and in all cardiac outputs were determined by the indicator-dilution technic. Pulmonary blood volume was estimated by the method of Newman employing the down slope of the dye-dilution curve.[22] All patients in the group with emphysema had unequivocal clinical and laboratory evidence of the disease. The miscellaneous cardiac group included many forms of acquired and a few cases of adult congenital heart disease. Most but not all, were compensated at the time of study.

RESULTS

Data were obtained from 9 normal subjects, 29 patients with pulmonary emphysema, and 80 patients with miscellaneous cardiac diseases. Figures 1 and 2 illustrate the 2 striking characteristics of the response to forced straining in emphysema: (1) marked narrowing of the terminal straining pulse pressure; and (2) marked prolongation of the time required for the post-straining systolic pressure to return to the control value. In table 1 the mean values relevant to these 2 characteristics are summarized for the 3 groups. Many of the patients with emphysema had virtually complete obliteration of the peripheral pulse during performance of the Valsalva maneuver. Figures 3 and 4 depict the types of responses to the Valsalva maneuver obtained from normal subjects and patients with severe heart disease.

Table 2 summarizes physiologic data obtained on the patients with emphysema in conjunction with the Valsalva test. The average hematocrit, venous pressure, and circulation time are in the high normal range. The severity of the pulmonary disease is indicated by a decrease in arterial oxygen saturation and reduction in the 3-second, vital capacity. Although the mean cardiac index for the entire

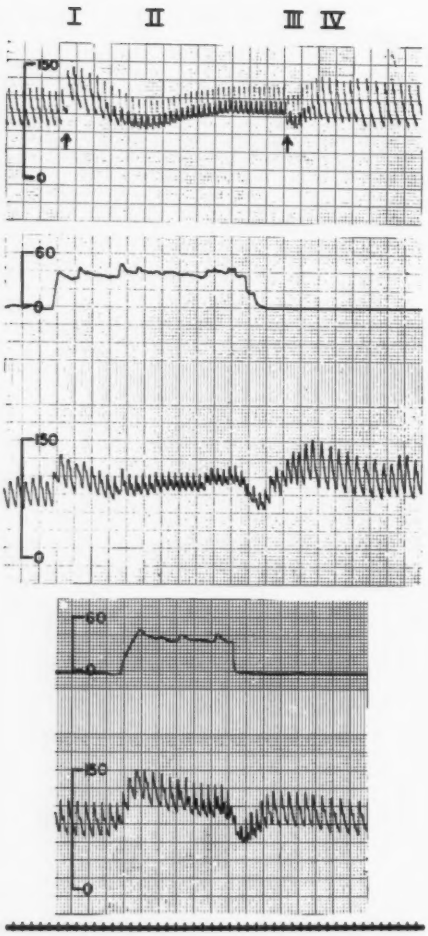

FIG. 3. Brachial arterial and intraoral pressures in 2 normal subjects (below) and arterial pressure alone in normal subject (above). Time marker is in seconds. Roman numerals indicate the 4 phases of the arterial pressure response to the Valsalva maneuver.

emphysema group is within normal limits, the 12 patients who had the most marked "emphysema responses" were those who had low cardiac outputs and low pulmonary blood volumes. Venous pressure and the degree of arterial oxygen unsaturation did not appear to be important as determinants of the intensity of the emphysema response.

Table 3 correlates cardiac index with the time required for the post-straining systolic

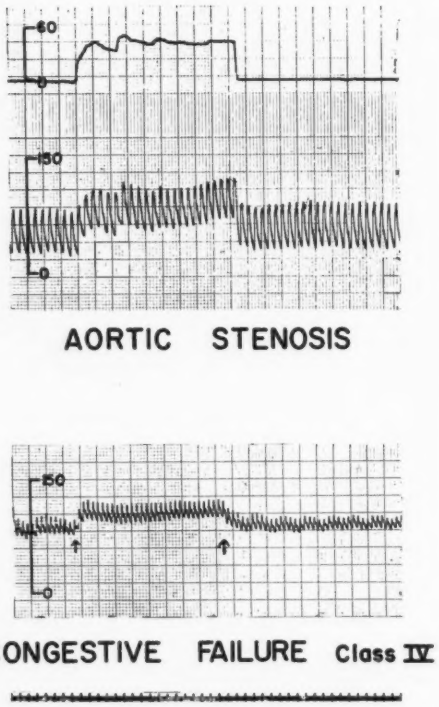

FIG. 4. Arterial pressure (below) and arterial pressure and intraoral pressure (above) in 2 patients with severe heart disease subjected to forced straining. Time marker is in seconds.

pressure to return to baseline. The lower the cardiac index, the longer is the time required for the return of systolic pressure to control level. Furthermore, 17 of 23 subjects with cardiac indices greater than 2.5 L./M.^{2} had distinct post-straining overshoots while only 1 of the 6 with cardiac indices below this level had a distinct overshoot.

DISCUSSION

The emphysema response to the Valsalva maneuver appears to be simply an exaggerated form of the normal response. It consists mainly of a sharp diminution of the cardiac output, in some cases almost to the vanishing point. A similar response can be brought about in the normal individual if the straining is forced to sufficiently high pressure. We have seen it in a few normal individuals who were able to force

TABLE 2.—*Physiologic Data Obtained on Twenty-nine Patients with Pulmonary Emphysema*

	No.	$\frac{\text{P.P.s}}{\text{P.P.c}} \times 100$*	Time required for post-straining systolic pressure to reach control (sec.)	Hematocrit	Arterial O_2 sat. (%)	V.P.† (mm. H_2O)	Circulation time‡ (sec.)	C.I.§	SIVI‖ (L./M.²)	3″ V.C.¶
Patients in whom terminal straining pulse pressure < 15 per cent of control.	12	8.8	13.8	47.8	88.9	119.6	17.9	2.58	.402	65
Patients in whom terminal straining pulse pressure > 15 per cent of control.	17	34.7	9.9	47.1[a]	87.4	102.2	16.5[a]	3.32	.585	64.6[b]
Mean.....	29	24.0	11.5	47.4	88.1	105.3	17.1	3.01	.495	64.8

* $\frac{\text{P.P.s.}}{\text{P.P.c.}} \times 100 - \frac{\text{Terminal straining pulse pressure}}{\text{Control pulse pressure}} \times 100.$

† V.P.—Venous pressure

‡ Circulation time—Time required for indicator to appear at sampling site in brachial artery after injection into brachial vein.

§ C.I.—Cardiac index = $\frac{\text{Cardiac output}}{\text{Body surface area}}$

‖ SIVI—Slope volume index = $\frac{\text{Slope volume}}{\text{Body surface area}}$, index of pulmonary blood volume.

¶ 3″ V.C.—3 sec. vital capacity, per cent of normal.

[a] 15 cases only

[b] 13 cases only

intrathoracic pressure above 60 mm. Hg. Dawson[9] reported that Weber succeeded in producing syncope and convulsions in himself, and he also gave an account of prisoners of ancient times using the same method to avoid torture.

Our data do not permit a definitive explanation of the exaggerated response in pulmonary emphysema, but one may speculate on several possible mechanisms. Failure of the cardiac output due to increased intrathoracic pressure may be caused by impingement of this pressure at several different sites. These might be the ventricular or atrial walls, the pulmonary vasculature, or the venae cavae.

High intrathoracic pressure could restrict the motion of the ventricles as in cardiac tamponade, or it might collapse the thin atrial walls. Neither of these 2 possibilities appears likely, since the pulse obliteration requires several seconds to reach a maximum after the pressure is applied. One would expect that if this mechanism were to operate, it would occur as soon as the pressure was applied.

It is possible that exertion of high pressure on the pulmonary blood vessels would narrow them to such an extent that the right ventricle would be unable to generate sufficient pressure to propel blood through them. This should cause acute dilatation of the right ventricle. We have no data on this point, but evidence bearing on the problem might be obtained by observing emphysema patients under fluoroscopy during the Valsalva maneuver.

Damming back the venous return to the right ventricle is known to be a major factor in the genesis of the normal response to forced straining. This is partially overcome by a rise of venous pressure above the intrathoracic pressure. It is possible that the veins of the emphysema patient are less reactive and less able to increase their pressures in response to the challenge of the Valsalva maneuver than are the veins of the normal subject. It is also

TABLE 3.—*Relationship between Cardiac Indices and Time Required for Post-Straining Systolic Blood Pressure to Return to Control Level in Patients with Emphysema*

	No. of cases	Average time required for post-straining systolic pressure to return to the control level (sec.)	No. of cases with distinct post-straining systolic overshoots greater than 10 mm. Hg
Cardiac index less than 2.5 L./M.²	6	16.3	1
Cardiac index 2.5–3.5 L./M.²	16	11.3	13
Cardiac index greater than 3.5 L/M.²	7	8.0	4

conceivable that barrel chest deformities in emphysema may expose more serosal surface area of the vena cava to the high intrathoracic pressure and thereby make it more susceptible to collapse.

Although the mechanisms leading to pulse obliteration remain obscure, our data provide some evidence to explain the delay in return to normal pressure following straining in the patient with emphysema. The rapid but not instantaneous decline in pulse pressure during straining and the slow recovery to control levels after release suggest that the lungs are probably emptied of their blood content more or less completely while pressure is being exerted. On release the right ventricle must first pump enough blood to fill the pulmonary vessels before enough can be delivered to the left ventricle to re-establish normal peripheral pulse pressure. It is significant that the cases showing the greatest delay in recovery were the ones with the lowest cardiac outputs and pulmonary blood volumes. It may be that those with higher pulmonary blood volumes were more resistant to having their lungs emptied of blood.

The post-straining overshoot was absent in several of the patients, particularly in the group with low cardiac output. Absence of the post-straining overshoot has been described as characteristic of congestive heart failure.[3, 19] In our cases, subclinical failure may have been present; however, the straining portion of our curves with a striking fall-off is entirely different from that observed in congestive failure in which there is a sustained rise in systolic pressure.

The mechanisms responsible for the emphysema response undoubtedly also account for the susceptibility of these patients to cough syncope, for coughing is but a series of Valsalva maneuvers.[23]

SUMMARY

In the majority of patients with pulmonary emphysema the forced straining of the Valsalva maneuver leads to a unique circulatory response.

This "emphysema response" has 2 characteristics: marked diminution in terminal straining pulse pressure frequently to the point of obliteration, and marked delay in the return of post-straining systolic pressure to the control level.

The emphysema response appears to be an exaggeration of the normal response to the Valsalva maneuver and is most marked in those patients with emphysema who have low cardiac output and small pulmonary blood volume.

SUMMARIO IN INTERLINGUA

In le majoritate de patientes con emphysema pulmonar le effortio del experimento de Valsalva produce un responsa circulatori de character unic.

Iste "responsa emphysematic" ha 2 characteristicas: marcate diminution—frequentemente al puncto de su obliteration—del pression del pulso al fin del effortio; e marcate retardation, post le effortio, in le retorno del pression systolic al nivello de controlo.

Le responsa emphysematic pare esser un exaggeration del responsa normal al experimento de Valsalva. Illo es le plus marcate in ille patientes con emphysema qui ha basse rendimento cardiac e parve volumine sanguinee pulmonar.

ACKNOWLEDGMENT

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REFERENCES

1 ELISBERG, E. I., SINGIAN, E., MILLER, G., AND KATZ, L. N.: The effect of the valsalva maneuver

on circulation. III. The influence of heart disease on the expected post straining overshoot. Circulation **7:** 880, 1953.

GOLDBERG, H., ELISBERG, E. I., AND KATZ, L. N.: The effects of the Valsalva maneuver upon the circulation in normals and patients with mitral stenosis. Circulation **5:** 38, 1952.

KNOWLES, J. H., GORLIN, R., AND STOREY, C. F.: Clinical test for pulmonary congestion with use of the Valsalva maneuver. J.A.M.A. **160:** 44, 1956.

[4] GREENE, D. G., AND BUNNELL, I. L.: The circulatory response to the Valsalva maneuver on patients with mitral stenosis with and without autonomic blockade. Circulation **8:** 264, 1953.

[5] MCINTOSH, H. D., BURNUM, J. F., HICKAM, J. B., AND WARREN, J. V.: Circulatory changes produced by the Valsalva maneuver in normal subjects, patients with mitral stenosis and autonomic nervous system alterations. Circulation **9:** 511, 1954.

[6] SHARPEY-SCHAFER, E. P.: Effects of Valsalva's maneuver on the normal and failing circulation. Brit. M. J. **1:** 693, 1955.

[7] YU, P. N., LOVEJOY, F. W., JR., JOOS, H. A., NYE, R. E., JR., BEATTY, D. C., AND SIMPSON, J. H.: Studies of pulmonary hypertension. VI. Pulmonary "capillary" pressures in various cardiopulmonary diseases at rest and under stress. Am. Heart J. **49:** 31, 1955.

[8] KATTUS, A. A., JR., AND MILLS, H.: The effect of forced straining (Valsalva's maneuver) in patients with pulmonary emphysema. Clinical Research Proceedings **4:** 67, 1956.

[9] DAWSON, P. M.: An historical sketch of the Valsalva experiment. Bull. Hist. Med. **14:** 295, 1943.

[10] FLACK, M., AND BURTON, H. L.: An investigation into the physiological significance of the "40 mm. mercury test." J. Physiol. **56:** 1, 1922.

[11] HAMILTON, W. F., WOODBURY, R. A., AND HARPER, H. T.: Physiologic relationships between intrathoracic, intraspinal and arterial pressures. J.A.M.A. **107:** 853, 1936.

[12] BUNNELL, I. L., GREENE, D. G., AND KUNZ, W. W.: Influence of tetraethylammonium chloride on the circulatory responses to the Valsalva maneuver. J. Appl. Physiol. **4:** 345, 1951.

[13] ELISBERG, E. I., MILLER, G., WEINBERG, S. L., AND KATZ, L. N.: Effect of Valsalva maneuver on circulation: Role of autonomic nervous system in production of overshoot. Am. Heart J. **45:** 227, 1953.

[14] SARNOFF, S. J., HARDENBERGH, E., AND WHITTENBERGER, J. L.: Mechanism of the arterial pressure response to the Valsalva test. The basis of its use as an indicator of interchange of sympathetic outflow. Am. J. Physiol. **154:** 316, 1948.

[15] BJORK, V. O., MALMSTROM, G., AND UGGLA, L. G.: Left atrial and pulmonary "capillary" pressure curves during Valsalva's experiment. Am. Heart J. **47:** 635, 1954.

[16] LEE, G., DE, J., MATHEWS, M. B., AND SHARPEY-SCHAFER, E. P.: The effect of the Valsalva maneuver on the systemic and pulmonary arterial pressure in man. Brit. M. J. **16:** 311, 1954.

[17] ELISBERG, E. I., GOLDBERG, H., AND SNIDER, G. L.: Value of intraoral pressure as a measure of intrapleural pressure. J. Appl. Physiol. **4:** 171, 1951.

[18] JUDSON, W. E., HATCHER, J. D., AND WILKINS, R. W.: Blood pressure responses to the Valsalva maneuver in cardiac patients with and without congestive failure. Circulation **11:** 889, 1955.

[19] SHARPEY-SCHAFER, E. P.: Effects of Valsalva's maneuver on the normal and failing circulation. Brit. M. J. **1:** 693, 1955.

[20] STUCKI, P., HATCHER, J. D., JUDSON, W. E., AND WILKINS, R. W.: Studies of circulation time during the Valsalva test in normal subjects and in patients with congestive heart failure. Circulation **11:** 900, 1955.

[21] BORROUGHS, R. W., AND BRUCE, R. A.: Significance of abnormal phase II response to Valsalva maneuver in cardiac patients. Circulation **14:** 72, 1956.

[22] NEWMAN, E. V., MERRELL, M. M., GENECIN, A., MONGE, C., MILNOR, W. A., AND MCKEEVER, W. P.: The dye dilution method for describing the central circulation. An analysis of factors shaping the time-concentration curves. Circulation **4:** 735, 1951.

[23] SHARPEY-SCHAFER, E. P.: The mechanism of syncope after coughing. Brit. M. J. **2:** 860, 1953.

Congenital Malformations of the Heart Associated with Splenic Agenesis

With a Report of Five Cases

By Enid F. Gilbert, M.B.B.S., Kinsuke Nishimura, M.B., and Bernice G. Wedum, M.D.

This paper presents a theory for the cause of congenital malformations of the heart and other structures associated with absence of the spleen. A complete review of the literature and the data of the authors' 5 cases lead to this proposal: a lethal factor, possibly the product of a faulty ovulation, specifically affects the germinal bed of the mesoblastic surface of the coelom at an ovulatory age of 24 to 28 days.

IT WOULD appear that congenital absence of the spleen is almost invariably associated with severe cardiac malformations. The purpose of this paper is to review the literature on this subject, to present 5 additional cases, and to postulate a theory of etiology based on embryologic development. The first detailed description of splenic agenesis was recorded by Pohlius[1] in 1740. The description of the heart, however, left some doubt whether a structural defect was present. Six reports[2-7] had appeared earlier, the first being those of Schenkius[2] and Hollerius.[3] Martin[8] and Breschet[9] described the first 2 cases of the association of splenic agenesis and defects of the heart and great vessels. A total of 81 cases of this combination has thus far been reported. Splenic agenesis is associated with anatomic malformations of the heart that include variations in systemic and pulmonary venous return, defects in the atrial and ventricular septa, anomalies of the truncus, pulmonary artery and valve, and atrioventricular orifice. Dextrocardia and anomalies of the abdominal viscera and lungs, resulting in bilateral symmetry or partial situs inversus, are frequently present.

Review of the Literature

Twenty-seven instances of absence of the spleen that were unassociated with intracardiac defects have been recorded in the literature.[1, 4, 6, 10-13, 14-33] In an additional 16 cases no specific mention of the heart was made in the autopsy findings,[2, 3, 5, 7, 34-45] making a total of 43. Partial situs inversus occurred in 8[11, 13, 14, 19, 26, 28, 29, 35] (including 1[11] in which there was separate drainage of the hepatic veins into the right atrium), and multiple congenital anomalies in 5 patients.[4, 6, 10, 12, 34] Prolonged chronic infection or neoplasia was the cause of death in 14 instances.[3, 7, 13, 15, 17, 18, 20-25, 27, 28] It would seem most probable in the latter that destruction of splenic tissue rather than agenesis accounted for the absence of the spleen.

Millar and Garrow[31] reported a 6-week-old infant with cyanosis since birth who was found at autopsy to have an enlarged heart, a right aortic arch, and an absent spleen. However, no intracardiac defect was present. This infant also showed a high percentage of normoblasts in the peripheral blood and bone marrow. An infant who died shortly after birth and who was found at postmortem examination to have a patent foramen ovale, symmetrical liver, and absence of the spleen was reported by Birch-Hirshfield.[16] One instance of congenitally absent spleen in a 9-month-old white female infant, dying as a result of purulent meningitis and showing no other anomalies at autopsy, was mentioned by Ivemark.[46]

Congenital absence of the spleen in association with congenital cardiac malformations has been reported in 81 cases[8, 9, 19, 33, 46-92] (table 1). The details of sex, age of patient, and character of lesions appear in this table. A marked

From the Department of Pathology of The Children's Hospital, Washington, D. C.

TABLE 1.—*Eighty-five Cases of Splenic Agenesis, Associated with Congenital Malformations of the Heart**

Year of publication and reference number	Age	Sex	Position of the heart	Congenital defects
1826[8]	6 wk.	?	L	ASD, ASVR, CAVV, VSD, TGV, PDA, TS, SL
1826[9]	?	?	D	ASD, ASVR, VSD, TGV, PA, PDA, SLL
1834[47]	8 da.	M	D	ASD, VSD, SV, TGV, TS, TL
1857[48]	20 da.	?	L	ASD, VSD, CB, TGV
1868[49]	15 wk.	F	D	ASD, ASVR, CAVV, VSD, CT, TGV, PA, PDA, APVR, SLL, TL
1875[50]	2 da.	M	L	ASD, ASVR, CAVV, VSD, SV, PA, APVR
1886[51]	5 wk.	F	L	ASD, ASVR, CAVV, VSD, TGV, APVR, SLL, TS, TL
1887[52]	1 mo.	?	D	ASD, VSD, SV, SLL, TS
1887[53]	5 wk.	M	D	TGV, PS, PDA, SLL
1888[54]	4 wk.	F	D	VSD, TGV, SL
1899[55]	6 mo.	M	D	ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, SLL, TS, TL
1899[19]	20 da.	?	L	ASD, ASVR, TGV
1901[56]	14 wk.	F	L	ASD, ASVR, VSD, SV, TGV, PDA, TS
1905[57]	1½ yr.	M	L	ASD, CAVV, VSD, PA, SLL
1905[57]	9 da.	M	D	ASD, ASVR, CAVV, VSD, SV, TA, APVR, SLL, SL
1908[58]	2½ mo.	M	L	ASD, CAVV, VSD, TGV, PS, SLL
1915[59]	4½ mo.	M	D	ASD, ASVR, SV, TGV, APVR, SLL, TL
1920[60]	9 mo.	?	L	ASD, VSD, SV, TS, SL
1922[61]	3 mo.	M	L	ASD, ASVR, VSD, APVR, SLL, TL
1926[62]	Newborn	?	L	ASD, CAVV, VSD, SV, TGV, PDA, APVR, SLL, TS, SL
1926[62]	6 mo.	M	L	ASD, ASVR, VSD, TGV, SLL, TS, TL
1927[63]	?	?	D	ASD, ASVR, VSD, SV, TA, APVR
1929[64]	7 mo.	M	L	ASD, ASVR, CAVV, VSD, SV, PS, APVR, SLL, TS, SL
1930[65]	4 mo.	F	D	ASD, ASVR, CAVV, VSD, SV, TGV, PS, SLL, TS, SL
1930[66]	3 mo.	M	L	ASD, VSD, TA, APVR, SLL
1930[67]	14 mo.	M	D	ASD, CAVV, VSD, SV, TA
1932[68]	2½ yr.	F	D	ASD, CAVV, VSD, TGV, PS, PDA
1932[69]	4 mo.	M	D	ASD, CAVV, VSD, PA, PDA, TS
1938[70]	6 mo.	F	D	ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, TS, SL
1938[71]	1 da.	M	L	ASD, ASVR, CAVV, VSD, TGV, PDA, SLL, TS, SL
1939[72]	2 mo.	M	L	ASD, CAVV, VSD, SV, TGV
1939[73]	6 mo.	F	L	ASD, ASVR, CAVV, VSD, CB, PA, PDA, APVR, SLL
1942[74]	43 hr.	F	L	ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR
1942[74]	1 mo.	M	L	ASD, ASVR, CAVV, VSD, TGV, PDA
1942[75]	9½ mo.	M	L	ASD, CAVV, VSD, SV, TGV, PA, PDA, SLL, TS, TL
1947[76]	Stillborn	F	D	ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR, SLL, TS
1949[77]	6 da.	M	L	ASD, CAVV, VSD, TGV, PA, PDA, APVR, SLL, TS, SL
1950[78]	3 yr.	M	D	ASD, ASVR, CAVV, VSD, SV, TGV, PS, TS, TL
1951†[79]	4 mo.	M	L	ASD, ASVR, CAVV, VSD, TGV, PA, PDA, APVR, SLL, TS, SL
1951[80]	10 wk.	F	L	ASD, ASVR, VSD, SV, TGV, PDA, APVR, SL
1952[81]	11 wk.	F	L	ASD, VSD, SV, TA
1952[81]	10 wk.	M	L	ASD, VSD, SV, TGV, PA, PDA, APVR, SLL, TS, SL
1952[82]	15 wk.	F	D	ASD, ASVR, CAVV, VSD, SV, TGV, PS, PDA, APVR, SLL
1952[83]	23 mo.	M	L	ASD, CAVV, VSD, PS, SLL, TL
1952[83]	1 yr.	M	D	ASD, CAVV, VSD, SV, PS, SLL
1952[83]	6 wk.	F	L	ASD, CAVV, VSD, SV, TGV, PS, PDA, SLL, SL
1952[83]	10 da.	F	L	ASD, CAVV, VSD, PA, PDA, SLL, TS, TL
1953[84]	27 da.	M	L	ASD, CAVV, VSD, SV, PA, PDA, SLL, SL
1953[85]	38 da.	F	L	ASD, VSD, TGV, PA, PDA, APVR, SLL, TS, SL
1953[85]	4 mo.	F	L	ASD, ASVR, VSD, TGV, PS, PDA, APVR, SL
1953[86]	4 yr.	F	L	ASD, VSD, SV, TGV, PS, SLL, TS, SL
1953[86]	8 yr.	M	L	ASD, CAVV, VSD, SV, TGV, PS, SLL, TS, SL

TABLE 1.—*Continued*

Year of publication and reference number	Age	Sex	Position of the heart	Congenital defects
1953[87]	5 yr.	M	L	AS[illegible] ASVR, CAVV, VSD, SV, TGV, PS, APVR, SLL, TS, SL
1954[88]	3 da.	M	D	ASD, ASVR, CAVV, VSD, CB, TA, PDA, APVR, SLL, TS, TL
1954[88]	1½ hr.	M	L	ASD, ASVR, CAVV, VSD, CB, TA, PA, PDA, APVR, SLL, TS, SL
1954[89]	Stillborn	M	L	VSD, SL
1954[89]	3 mo.	F	D	ASD, ASVR, CAVV, VSD, TGV, PA, PDA, SLL
1955[33]	7½ mo.	M	D	ASD, ASVR, CAVV, VSD, CB, TGV, PA, PDA, APVR, SLL, TL
1955[90]	7 mo.	M	L	ASD, ASVR, VSD, TGV, PA, PDA, APVR, SLL, TS, TL
1955[91]	7 da.	F	D	CAVV, VSD, SV, PA, PDA, APVR, SLL
1955[46]	Stillborn	M	L	ASD, CAVV, VSD, SV, TA, APVR, SLL, SL
1955[46]	3 da.	M	L	ASD, ASVR, CAVV, VSD, SV, TA, SLL, TS, TL
1955[46]	4 wk.	F	L	VSD, SV, TA, APVR, SL
1955[46]	1 mo.	F	L	ASD, ASVR, CAVV, VSD, SV, TGV, PS, APVR, SLL, TS, SL
1955[46]	2 mo.	F	L	ASD, CAVV, VSD, TGV, PDA, TS, SL
1955[46]	15 wk.	F	D	ASD, ASVR, CAVV, VSD, SV, TGV, PA, PDA, APVR, SLL, SL
1955[46]	4 mo.	M	L	ASD, CAVV, VSD, SV, PS, TS, SL
1955[46]	4 mo.	F	L	ASD, ASVR, CAVV, VSD, SV, TGV, APVR, SLL, SL
1955[46]	4 mo.	M	L	ASD, CAVV, VSD, TGV, PA, PDA, SLL, TS, SL
1955[46]	5 mo.	M	D	ASD, CAVV, VSD, SV, TA, APVR, SLL, TS, TL
1955[46]	6 mo.	M	L	ASD, ASVR, CAVV, VSD, SV, TGV, APVR, SLL, SL
1955[46]	9 mo.	M	L	ASD, ASVR, CAVV, VSD, SV, TGV, PA, APVR, SLL, TS, TL
1955[46]	10 mo.	M	L	ASD, ASVR, CAVV, VSD, TGV, PS, APVR, TS, SL
1955[46]	2½ yr.	F	D	ASD, ASVR, VSD, TGV, PS, APVR, TS, SL
1956[92]	2 mo.	M	L	ASD, CAVV, VSD, CT, TGV, PDA, SLL, TS, TL
1956[92]	18 da.	M	L	CAVV, VSD, CT, PA, PDA, SLL, SL
1956[92]	7½ mo.	M	L	ASVR, VSD, CT, TGV, PA, APVR, SLL, TS, TL
1956[92]	15 hr.	F	D	ASD, TS
1956[92]	Prem.	F	L	ASD, ASVR, VSD, PDA, APVR, TS, TL
1956[92]	5 mo.	M	L	ASD, VSD, CB, TGV, PS, SLL
1956[92]	36 hr.	F	L	ASD, ASVR, CAVV, VSD, CB, TA, APVR
1957‡	2½ yr.	F	D	ASD, ASVR, CAVV, VSD, TGV, PS, APVR, SLL, TL
1957‡	6 da.	F	L	ASD, CAVV, TGV, PA, PDA, SLL, SL
1957‡	8 mo.	F	L	ASD, ASVR, CAVV, VSD, SV, TGV, PDA, APVR, SLL, TS, SL
1957‡	20 da.	F	L	ASD, ASVR, CAVV, VSD, SV, TA, APVR, SLL, TS, SL

*A more detailed form of this table has been deposited as Document number 5328 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $2.50 for photoprints or $1.75 for 35 mm. microfilm. Advance payment is required. Make checks payable to: Chief, Photoduplication Service, Library of Congress.

† Refers to case 1 of the authors' series.

‡ Refers to cases 2, 3, 4, and 5, of the authors' series.

ASD = atrial septal defect; ASVR = anomalous systemic venous return; CAVV = common atrioventricular valve; VSD = ventricular septal defect; SV = single ventricle; CB = cor biloculare; CT = cor triloculare; TA = truncus arteriosus; TGV = transposition of great vessels; PA = pulmonary atresia; PS = pulmonary stenosis; PDA = patent ductus arteriosus; APVR = anomalous pulmonary venous return; SLL = supernumerary lobulation of the lungs; TS = transposition of the stomach; TL = transposition of the liver; SL = symmetrical liver.

The defects not listed were either not present or not mentioned in the report.

tendency toward a symmetrical disposition of the abdominal viscera was strikingly frequent. The liver was transposed in 22 cases, the left lobe was equal in size to the right lobe in 32 cases, larger than the right lobe in 1, and had abnormal lobes in 1. Dextroposition of the stomach occurred in 41 instances and a common mesentery was present in 35 cases. Minor degrees of displacement of the duodenum or pancreas were mentioned infrequently. The presence of a primitive dorsal mesogastrium and absence of the greater omentum was em-

ABLE 2.—*Developmental Horizons with Corresponding Length and Age of the Human Embryo (from Streeter)*[32]

Horizon	Length of embryo (mm.)	Age of embryo (days)
XI	2.5–3.0	24 ± 1
XII	3.5	26 ± 1
XIII	4–5	28 ± 1
XIV	6–7	28–30
XV	7–8	31–32
XVI	9–10	33 ± 1
XVII	11–13.6	35 ± 1
XVIII	14–16	37 ± 1

phasized in the 2 cases reported by Durie and Wyndham.[74]

There were, in addition, 6 cases of spina bifida or maldevelopment of the vertebrae[9, 52, 75, 84, 86 case 3, 92 case 100,748] 7 cases of anomalies of the branches of the abdominal aorta,[8, 51, 57, 62 cases 4 and 5, 64, 71] 7 cases of anomalies of the urogenital system, [46 case 7, 57, 66, 89 case 2, 90, 92 case 524,038, our case 4] 3 cases of dextroposed esophagus, [46 case 7, 52, 69] 2 cases of anal atresia,[66, 88] and 1 each of hydrocephalus,[78] harelip,[47] Meckel's diverticulum,[83 case 3] torticollis,[85] absence of the tail of the pancreas,[89 case 2] absence of the gallbladder and clubbing of the phalanges,[46 case 7] aplasia of the left diaphragm,[92 case 100,748] and stenosis of the rectum.[57]

Recently 4 cases have been reported in which an antemortem diagnosis, confirmed later at autopsy, was made on the basis of the hematologic morphology.[33, 90] The presence of Heinz-Ehrlich bodies, Howell-Jolly bodies, target cells, and nucleated red cells in the peripheral blood and siderocytosis as well as erythroid hyperplasia in the bone marrow appeared to be a constant feature. Two other cases reported by Willi and Gasser[33] (cases 3 and 5) were diagnosed during life by hematologic studies as well as by angiocardiography and cardiac catheterization.

Embryology

The developmental horizons with the corresponding length and age of the human embryo are presented in Table 2.

Early splenic primordia, consisting of a mesenchymal thickening in the dorsal mesogastrium are present when the developing embryo has an ovulatory age of 31 to 35 days (horizons XV-XVII; 9-12 mm.).[46] During the same period, fusion of the anterior and posterior endocardial cushions with the margin of the septum primum causes obliteration of the foramen primum and partitioning of the atrioventricular canal.[93, 94] Complete division of the truncus is accomplished at 35 days (horizon XVII; 11-13.6 mm.).[95]

The septum primum can be identified at 26 days (horizon XII; 3.5 mm.). The cephalic portion shortly thereafter undergoes resorption with the formation of the foramen secundum, with the septum secundum making its appearance at 35 days. Division of the ventricle begins at 31 days (horizon XV; 7-8 mm.) as an anteroposterior muscular ridge in the floor of the bulboventricular cavity. Aortic and pulmonary semilunar valves are formed at 35 days. Venous drainage from the cephalic portion of the embryo is via the right and left anterior cardinal veins; these veins join into the common cardinal veins and drain into the sinus venosus.[96] At 33 days (horizon XVI; 9-10 mm.) the left common cardinal vein courses down posteriorly and eventually becomes absorbed to form the coronary sinus.[94] A persistent left superior vena cava results from persistence of the left anterior cardinal vein.

Venous drainage from the caudal portion of the embryo is through 3 groups of veins: the posteardinal, the vitelline, and the omphalomesenteric. The posterior cardinal veins undergo several modifications and are eventually completely replaced in their abdominal course by the subcardial veins. The upper portion contributes to the formation of the inferior vena cava, the lower to the formation of the common iliac veins. The right and left vitelline veins are connected both ventrally and dorsally to the duodenum. When the stomach and duodenum rotate from their midsagittal position, which occurs between 31 and 35 days[97] (horizons XV-XVII; 7-13.6 mm.), the blood in the right vitelline vein tends to flow across the ventral anastomotic plexus to the left vitelline vein. The left vitelline vein in turn sends its blood directly to the liver by

way of a dorsal anastomosis with the hepatic end of the persistent part of the right vitelline vein.[96] Failure of rotation of the stomach and duodenum may account for the persistence of both vitelline veins and their independent drainage into the right atrium. The umbilical veins pass into the liver where they form sinusoids and freely communicate with the vitelline system at 31 days (horizon XV; 7-8 mm.). At 34 days the right umbilical vein atrophies and disappears. The left umbilical vein becomes incorporated into the ductus venosus.

Early pulmonary venous channels are derived from the splanchnic plexus, which drains into the precardinal and postcardinal veins as well as the umbilicovitelline system. At this stage the primordia of the lungs have no direct connection with the heart. To the left of the septum primum an outpouching occurs that extends toward the developing lungs and makes connection with that portion of the splanchnic plexus related to the lungs.[98] As the pulmonary veins are incorporated into the developing left atrium, the main anastomosis of the pulmonary vessels with the cardinal and umbilicovitelline venous systems is interrupted. This development of the pulmonary venous system has been observed in embryos between 21 and 30 days[98] (horizons X-XIV; 2-7 mm.). Abnormal positioning of the atrial septum with displacement of the septum primum to the left may account for anomalous connections of the pulmonary veins with the right atrium.[99]

Case Reports

Case 1

A. L. This 4-month-old Negro male infant was first admitted at 5 days of age because of cyanosis of lips and circumoral region. The family history was noncontributory. The pregnancy and labor were uneventful. The birth weight was 7 pounds, 2 ounces.

The physical findings of significance on admission were limited to the cardiovascular system. There was circumoral cyanosis. The heart rhythm was regular. The first heart sound was of normal intensity and the second sound was markedly accentuated and extraordinarily pure. No murmurs were heard. The blood pressure in the upper extremities was 72/48. The femoral pulsations were present bilaterally.

A hemogram showed a red blood count of 4.9 million per mm.^{3} with 20 Gm. of hemoglobin. The white blood count was 14,000 per mm.^{3} with 48 per cent neutrophils, 1 per cent eosinophils, and 51 per cent lymphocytes. There were 34 nucleated red blood cells per 100 white blood cells. The urinalysis was negative. An anteroposterior roentgenogram of the chest revealed a heart of normal size. The contour was abnormal with a tipped-up apex and a widening of the great vessel shadow, making a rather sharp angle at its junction with the heart. The vascularity of the lung fields was markedly decreased and the gas bubble in the stomach was on the right side. A barium swallow verified the dextroposition of the stomach without dextrocardia or displacement of the esophagus. An electrocardiogram showed normal sinus rhythm at 150 per minute, P-R interval of 0.12 second, QRS duration of 0.06 second, and right axis deviation. The R wave in V_1 measured 16 mm. and in V_5, 8 mm. There was right ventricular preponderance.

The infants' course was characterized by progressive increase in cyanosis terminating in congestive failure and death at 9 months of age.

Pertinent Autopsy Findings. The major portion of the heart lay to the left of the midline. Both lungs had 3 lobes. The right and left lobes of the liver were of approximately equal size, but the inferior vena cava had an abnormal position to the left of the quadrate lobe. The gallbladder lay beneath the right lobe of the liver in a normal position. The stomach was dextroposed, the duodenum passing to the left. The majority of the pancreas lay to the right of the midline with the tail extending to the right and the head lodged in the curve of the duodenum. The ileocecal junction was in the right lower quadrant. A careful search for the spleen failed to reveal any splenic tissue. The splenic artery and vein were also absent.

Description of the Heart. The major portion of the heart (fig. 1) lay in the left chest. The right atrium was somewhat dilated and hypertrophied. There was a right-sided superior vena cava that drained into the right atrium and the 2 right hepatic veins arose from the posterior surface of the liver and entered the right atrium in the position usually occupied by the inferior vena cava. The coronary sinus was not present, but numerous openings of small coronary veins were seen in both atria.

There was a defect in the atrial septum measuring 0.5 cm. in diameter and a large defect existed among all 4 chambers that measured 2 cm. in diameter. The common orifice between the atria and ventricles was guarded by a single large valve

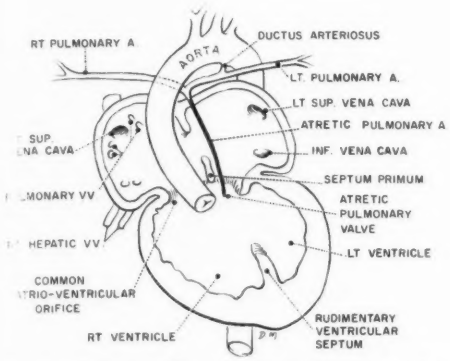

FIG. 1. Case 1. Schematic illustration of the heart.

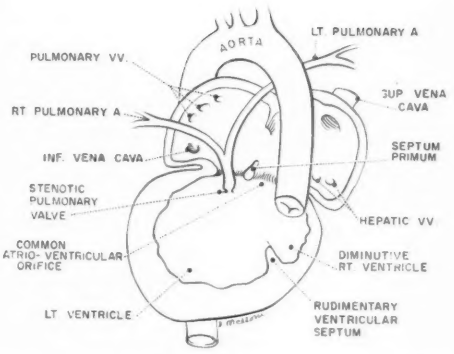

FIG. 2. Case 2. Schematic illustration of the heart.

consisting of 3 cusps; a large anterior, a large posterior, and a small lateral cusp.

A rudimentary ventricular septum was present somewhat to the left of its usual position.

Both ventricular walls were hypertrophied, measuring 1 cm. in thickness. There was complete atresia of the pulmonary valve and the pulmonary artery was a fibrous cord, measuring 0.2 mm. in diameter, originating posterior to its normal position and to the left of the aorta. The lumina of the major branches of the pulmonary artery were patent at its bifurcation, and measured 3 mm. in diameter. The ductus arteriosus was patent and united with the left pulmonary artery. The aorta arose anterior and to the right of its usual position, receiving blood from both ventricles. Three semilunar valves were present. The ostia of the coronary arteries were in their usual position. The innominate, left carotid, and left subclavian arteries arose in this order from the arch of the aorta, which descended on the left. All 4 of the pulmonary veins drained into the right atrium. A persistent left superior vena cava and a left-sided inferior vena cava, which received the left hepatic veins, entered a small left atrium.

Microscopic examination showed extramedullary hematopoiesis of the liver.

The pathologic diagnoses are summarized in table 1.

Case 2

J. L. This white female infant was first admitted at the age of 10 months because of fever and cough for 3 days. The infant was the product of a first uncomplicated pregnancy and was born at term, weighing 6 pounds, 4 ounces. Cyanosis became apparent at about 4 weeks of age. There had been frequent episodes of fever, respiratory infection, and difficulty in breathing. Both parents were living and well and there was no family history of any serious illnesses.

The physical findings of significance were limited to the cardiovascular system. Cyanosis and clubbing of the fingers and toes were present. There was a slight right precordial bulge, the point of maximum intensity was in the fifth right intercostal space and the rhythm was regular. The blood pressure was not recorded. There was a harsh systolic murmur heard best over the apex and that extended throughout systole. The murmur was transmitted to both axillae, the back, and the entire precordium. Diastole was clear. There were good femoral pulses.

Urinalysis was negative. The hemoglobin was 14.0 Gm. per 100 ml., the leukocyte count was 26,000 per mm.^{3} with 38 per cent polymorphonuclear cells and 62 per cent lymphocytes. An anteroposterior roentgenogram of the chest revealed a heart to be on the right and not enlarged. There was straightening of the left border in the position usually occupied by the right atrium in a dextrocardia, and the great vessel shadow at the base was narrowed. There was slight decrease in the vascularity of the lung fields. The liver was on the left side of the abdomen. An electrocardiogram revealed regular sinus rhythm with a rate of 155 per minute and a P-R interval of 0.15 second. The P waves in lead I were inverted. In aV_R the main deflection was upright and the T waves were diphasic. The QRS complex was diphasic in aV_L with inverted T waves. The infant's condition progressively deteriorated and she died at 2½ years of age.

Pertinent Autopsy Findings. The major portion of the heart lay on the right side of the thorax. The left lung was divided into 3 lobes with an additional small accessory lobe. The right lung was normally lobulated. The larger lobe of the liver was on the left side of the abdomen as was the gallbladder. The stomach was on the left side. The cecum and appendix were

located in the left iliac fossa. No spleen or splenic vessels were identified.

Description of the Heart. The heart (fig. 2) and lungs together weighed 375 Gm. The apex of the heart was on the right side of the thorax. There was a functional single atrium, the atrial septum being formed by the septum primum, which was 1 cm. in length. No septum secundum was present. The superior vena cava drained into the inferior portion of the right side of the atrium. Two left hepatic veins drained separately into the inferior portion and left side of the atrium. The coronary sinus was absent. There was a common atrioventricular orifice guarded by a single valve having 3 cusps consisting of a large anterior, a posterior, and a small lateral cusp. A rudimentary ventricular septum divided the heart into a diminutive right ventricle from which the aorta arose, and a larger left ventricle from which the pulmonary artery arose. The pulmonary valve was bicuspid with marked pulmonary stenosis. The aortic valve was formed by 3 cusps and both coronary arteries were present. The vessels of the right-sided aortic arch were normally situated for a dextrocardia, the right subclavian, right common carotid, and the innominate arteries arising in that order from right to left. The ductus arteriosus was closed. Two pulmonary veins drained the right lung and entered the right side of the atrium separately. Only 1 small pulmonary vein drained the left lung and this vessel entered the right side of the atrium posteriorly.

Microscopic examination revealed extramedullary hematopoiesis of the liver and lymphoid hyperplasia of the lymphatic tissues.

The details of the pathologic findings are summarized in table 1.

Case 3

M.H. This Negro female infant was the product of a normal full-term pregnancy and normal delivery. The birth weight was 6 pounds, 10 ounces. Cyanosis was first noticed 6 hours after delivery; it gradually became more intense and on the second day of life the infant was admitted to the hospital. The family history was noncontributory.

The relevant physical findings included moderate cyanosis, heart sounds of normal quality and intensity without murmurs, and a liver palpable 2 cm. below the right costal margin. The hemoglobin was 20.2 Gm. per 100 ml.; hematocrit reading 68 per cent; the leukocyte count 5,200 per mm.^{3}; polymorphonuclear cells 38 per cent, lymphocytes 55 per cent, and monocytes 7 per cent. The platelets were adequate. There were 244 nucleated red cells per 100 white cells. The sickling preparation was negative. An electrocardiogram revealed regular sinus rhythm, rate 150 per minute, P-R interval 0.13 second, QRS duration 0.05 second. There were prominent P waves in the right-sided chest leads and low T waves in the limb leads. Four days after admission she became more cyanotic, developed respiratory distress, and died.

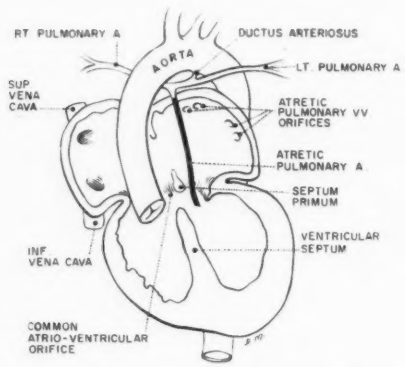

FIG. 3. Case 3. Schematic illustration of the heart.

Pertinent Autopsy Findings. The heart was in the midline being partially displaced to the right side with the apex directed to the left. The left lung consisted of 2 large and 2 smaller accessory lobes. The liver occupied a central position beneath the diaphragm, the left lobe being almost as large as the right lobe. The gallbladder was in its normal location on the right side. The stomach and entire gastrointestinal tract were normally located. Careful search for the spleen revealed no trace of splenic tissue or splenic vessels.

Description of the Heart. The heart (fig. 3) weighed 20 Gm. There was a functional single atrium. The septum primum was well formed but there was only a lacy vestige of the margin of the septum secundum leaving a large atrial septal defect measuring 1.4 by 1.1 cm. Both superior and inferior venae cavae were large and drained into the right side of the atrium. The coronary sinus was present. A common atrioventricular valve measured 4.6 cm. and consisted of 3 cusps: a large anterior cusp, a smaller posterior cusp over the crest of the ventricular septum, and a small lateral cusp. The ventricular septum was normally formed. The great vessels were transposed, the aorta arising from the right ventricle. The coronary artery orifices were normally situated. The pulmonary artery was represented by a thin fibrous strand of tissue that terminated in the ductus arteriosus. There was complete atresia of the pulmonary valve. A large patent ductus arteriosus bearing a normal relationship to the vessels of the left-sided aortic arch communicated with the right and left pulmonary arteries. All the pulmonary veins were extraordinarily small and drained into

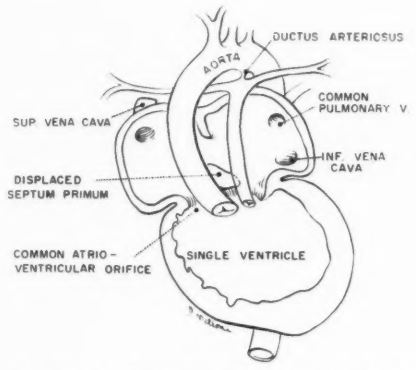

FIG. 4. Case 4. Schematic illustration of the heart.

the left side of the atrium. The pulmonary vein orifices were atretic.

Microscopic examination showed extramedullary hematopoiesis of the liver and the bone marrow contained an increased number of nucleated red cells. There was a moderate degree of lymphoid hyperplasia.

Table 1 summarizes the autopsy findings.

Case 4

M.C. This 7½-month-old Negro female infant was first admitted at 6 months of age, because of a respiratory infection of 1 week's duration. The family history was noncontributory.

Physical findings of significance were related to the cardiovascular system. The pulse rate was 160 and the respiratory rate was 56 per minute. There were circumoral cyanosis and clubbing of the fingers. The point of maximal impulse of the heart beat was in the fourth intercostal space in the left midclavicular line. The rhythm was regular, the heart sounds were of normal intensity, and a systolic murmur was heard in the left precordial, apical, and third intercostal regions. The blood pressure in the upper extremities was 90/65 and there were good femoral pulsations.

A hemogram revealed a hemoglobin of 8.7 Gm. per 100 ml., a hematocrit of 35 per cent, a leukocyte count of 11,700, with 32 per cent segmented cells, 2 per cent band forms, 62 per cent lymphocytes, and 2 per cent eosinophils. The platelet count was normal. The erythrocytes showed a moderate hypochromia, marked anisocytosis, poikilocytosis, many target cells, moderate polychromasia, and 119 nucleated erythrocytes per 100 leukocytes. No sickling was seen. An anteroposterior roentgenogram of the chest revealed the heart to be somewhat enlarged, especially to the left, with a globular contour and relative narrowing of the great vessel shadow at the base. In the left anterior oblique position there was a slight bulge in the anterior contour in the position usually occupied by the right atrium and definite enlargement of the left ventricle posteriorly. A clear aortic window was not seen. The vascular markings of the lungs were moderately increased. On fluoroscopic examination the pulmonary markings appeared decreased, with right ventricular and possibly right atrial enlargement. Dextroposition of the stomach was demonstrated by an upper gastrointestinal series. An electrocardiogram showed regular sinus rhythm, a pulse rate of 150 per minute, P-R interval of 0.12 second, and QRS duration of 0.05 second. There were fairly equal R and S waves in V_1 and upright T waves. The infant's condition deteriorated and she died at 7 months of age.

Pertinent Autopsy Findings. The heart together with the lungs weighed 276 Gm. The right lung was normally lobulated but the left lung had 3 lobes. The liver was markedly enlarged and overlaid the major portion of the dextroposed stomach. The left lobe was larger than the right lobe. The vermiform appendix was located in the right iliac fossa and the cecum was elongated and mobile. No spleen or splenic vessels were identified. There were 2 ureters arising from the left kidney.

Description of the Heart. The heart (fig. 4) was on the left side. There was a functional single atrium, the only evidence of an atrial septum being a septum primum, which was markedly displaced to the left. It was broad on the posterior aspect and narrow on the anterior aspect. There was no septum secundum. The superior vena cava was in its usual position and drained into the right side of the single atrium; the inferior vena cava drained into its left side. The coronary sinus was absent. There was a common atrioventricular orifice measuring 8.6 cm. consisting of 5 cusps, 1 very large anterior cusp, 1 smaller posterior cusp, and 3 additional diminutive cusps, all of which appeared to be displaced to the right in a clockwise direction. The endocardial cushions were displaced to the right and were represented by the 2 larger cusps. Both great vessels lay side by side, the aorta arising from the right side and the pulmonary artery from the left side of the single ventricle. The aortic and pulmonary valves measured 2.9 cm. and 3.3 cm. respectively, each consisting of 3 cusps and having 3 semilunar valves. There was no division of the ventricles except by a small muscular ledge that arched anteriorly between the orifices of the great vessels; no rudimentary outlet chamber was present. The ductus arteriosus was patent and measured 0.2 cm. in diameter at its pulmonary orifice. The vessels of the left-sided aortic arch were normally situated. All the pulmonary veins converged into

a single vessel that drained into the left side of the atrium.

Microscopic examination showed extramedullary hematopoiesis of the liver and an increased number of nucleated red cells in the sections of the bone marrow. There was a moderate degree of lymphoid hyperplasia.

The pathologic diagnoses are summarized in table 1.

Case 5

K.W. This white female infant was admitted to the hospital at 3 weeks of age because of cyanosis since birth. There was no relevant family history. The birth weight was 9 pounds and the delivery was uncomplicated. Respiratory difficulty and cyanosis became progressively worse until admission.

The relevant physical findings were as follows: The heart was regular, there was cardiac enlargement to the left, and a harsh systolic murmur was heard over the entire precordium, loudest over the left lower sternum. There was a questionable systolic thrill in the fourth left intercostal space. The peripheral pulses were weak. The blood pressure was not recorded. There was 2 plus pitting edema of the lower extremities and puffiness of the eyes and face. The liver was palpable 5 cm. below the right costal margin. The hemoglobin was 14.4 Gm. per 100 ml., red blood cell count 4.88 million per $mm.^3$, white blood cell count 16,678 per $mm.^3$ with a differential count of 66 per cent polymorphonuclear cells, 32 per cent lymphocytes, and 2 per cent monocytes. There were 62 nucleated red cells per 100 white blood cells. An anteroposterior roentgenogram of the chest revealed the heart to be enlarged both to the left and to the right with a tipped-up apex and a widened great vessel shadow, which made an abrupt angle at its junction with the heart. The vascularity of the lung fields was moderately decreased. An electrocardiogram revealed a regular sinus rhythm of 150 per minute and a P-R interval of 0.12 second. The P waves were flat in lead I and upright in leads II and III. There was marked left axis deviation. The T waves were flat in lead I and slightly upright in leads II and III. The precordial leads were normal. The patient was digitalized and operation was planned for the morning following admission, but during the night the patient died.

Pertinent Autopsy Findings. The heart lay on the left side and each lung had 3 lobes. The liver was central in position, the largest lobe being on the right. The gallbladder was in a central position. The stomach was on the right side under the liver. The duodenum consisted of 1 small loop that was short, joining quickly with the jejunum. The head of the pancreas was on the left side

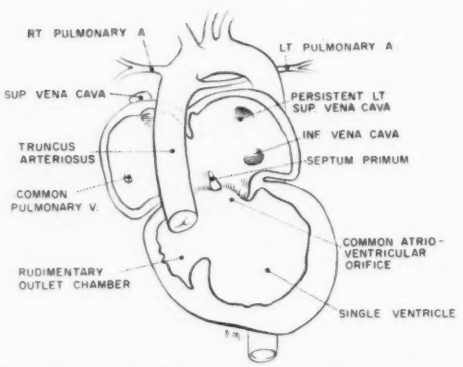

FIG. 5. Case 5. Schematic illustration of the heart

and the tail extended to the right. The small bowel appeared normal but was on the right side of the abdomen with the ascending colon being completely mobile and to the left of the small bowel. No spleen or splenic vessels were found in the abdominal cavity.

Description of the Heart. The heart (fig. 5) and lungs together weighed 210 Gm. There was a functional single atrium with no septum secundum. The only evidence of an atrial septum was a triangular-shaped septum primum, which was normal in position with its base inserted dorsally and the apex ventrally in the midline of the common cavity formed by the 2 atria. The superior vena cava was in its usual position and the inferior vena cava in addition to a persistent left superior vena cava drained into the left side of the septum primum. The coronary sinus was absent. There was a common atrioventricular valve consisting of 3 cusps, a large anterior, a large posterior, and a small lateral cusp. The single atrium communicated by way of the common atrioventricular orifice with a single ventricle that in turn communicated with a rudimentary outlet chamber from which a persistent truncus arteriosus arose. The valve was formed by 3 cusps; both coronary arteries were present. There was no main pulmonary artery; the right and left pulmonary arteries arose directly from the common trunk and the ductus arteriosus was absent. The vessels of the left-sided arch were normally situated. All pulmonary veins converged into 1 large vessel that drained into the atrium to the right of the septum primum.

Microscopic examination of the liver showed a slight degree of extramedullary hematopoiesis.

A summary of the autopsy findings is in table 1.

Discussion of Cases Reported

These 5 cases are remarkable in their similarity both to each other and to those previously reported

n the literature.

Levocardia was present in 4 and dextrocardia in 1. A functional single atrium was present in all cases and was associated with a single ventricle in 2. A common atrioventricular valve as well as anomalies of the cono-truncus region were features common to all cases, a truncus arteriosus occurring in 1 and transposition of the great vessels in 4. Of the latter, 2 were associated with pulmonary atresia, 1 with pulmonary stenosis, and 1 with a normal pulmonary artery. Total anomalous pulmonary venous return was present in 3 instances; in 1, the orifices of the pulmonary veins were atretic; and in 1, a single common pulmonary vein drained into the left side of the common atrium. The systemic venous return was anomalous in 4 cases; in case 1 a persistent left superior vena cava as well as a left inferior vena cava, which received 2 hepatic veins, drained into the left side of the atrium; in case 2 the superior vena cava as well as 2 hepatic veins drained separately into the left atrium while the inferior vena cava joined the right atrium; in case 4 the inferior cava drained into the left atrium, while in case 5 a persistent left superior vena cava as well as the inferior vena cava drained into the left atrium. The coronary sinus was absent in cases 1 and 4.

Supernumerary lobulation of the left lung as well as partial situs inversus with a marked tendency toward bilateral symmetry was common to all cases. Extramedullary hematopoiesis in the liver as well as erythroid hyperplasis of the bone marrow were also constant findings. A normoblastemia of the peripheral blood was seen in cases 1, 3, 4, and 5.

Four cases occurred at Children's Hospital, Washington, D. C., between 1951 and 1955 in an autopsy series of 676. One incompletely documented case of levocardia and partial situs inversus associated with splenic agenesis came to autopsy in 1948, making a total of 5 cases in an autopsy series of 3,526 during the period 1932 to 1955.

Electrocardiography. Vector analyses were done on the electrocardiograms by Dr. Robert Grant. Although electric forces from the atria were directed downward in cases 2, 3, and 5 and apparently also in case 1 rather than obliquely as when the atria are entirely normal, there was no evidense of atrial inversion. The electric forces reflected instead the anatomic symmetry that was present. The QRS forces were directed upward and to the right in case 2 suggesting abnormality of the crista supraventricularis, which was in this case hypertrophied. They were directed to the left in case 5, but the absence of the crista supraventricularis and presence of a single ventricle in this case could not be discerned from the contour of the vector loop.

Discussion

Examples of splenic agenesis with malformations of the heart and great vessels together with partial situs inversus fall into a fairly uniform anatomic pattern.

Agenesis of the spleen was considered by Putschar[26] to be the result of arrested development. Studies of the cardiac malformations that occur in association with splenic agenesis reveal anomalies of structures that would be developing during early splenic organogenesis. Ivemark[46] in an extensive study drew the general conclusion that a teratogenic action on the heart takes place simultaneously with resulting developmental arrest.

Gasser and Willi[81] considered the underlying causative mechanism to be an endogenous lethal factor.

The problem of partial or total situs inversus with a constant tendency toward visceral symmetry has been discussed by Toldt,[19] Geipel,[55, 100] and Tondüry[101] and was extensively studied by Törgersen.[102-104]

Forgaes[105] postulated a theory for the cardiac malformations associated with abdominal situs inversus. He made the observation that when either the abdominal viscera or the heart is transposed there is usually inversion of the atria. The right horn of the sinus venosus grows rapidly in early embryonic life, eventually forming part of the right atrium. Abdominal venous channels shunt blood from the left side of the abdomen to the opposite side, so that the venous drainage is to the right horn of the sinus venosus via the vena hepatis communis. Reversal of the normal relationship between the heart and liver would cause a reversal of the process with the left horn of the sinus venosus receiving the venous return from the abdomen, and the inferior vena cava eventually terminating in the left atrium. Forgaes therefore postulated that the associated malformations result as a faulty development of the cardiac septa or of an incomplete torsion of the aortopulmonary septum in an attempt to divert the venous return into the correct outflow channel.

Several investigators have stressed the importance of spiralling blood currents as being

responsible for the septation of the conotruncus; Doerr[106-107] postulated a "conflict zone" or intimate relationship between the cono-truncus and the atrioventricular canal in an attempt to explain simultaneous developmental errors occurring at both sites. Atrioventricular anomalies are always associated with malformation of the cono-truncus region in the series under discussion.

From a study of monographs, models, sections, and serial photomicrographs at the Carnegie Institute of Washington, Department of Embryology, the most probable explanation for this combination of lesions appears to be a factor with a wide lethal range operating at about an ovulatory age of 24 days (horizon XI; 2.5-3.0 mm.). This factor in its mildest form causes only a suppression of the development of the spleen, as in Ivemark's[46] case A-25-167 from the Boston Children's Hospital but in its most severe form an arrest in the development of the entire germinal bed of the mesoblastic surface of the coelomic cavity (Streeter,[95] fig. 3 XI, p. 29). As a result there is suppression of the development of the spleen and omental bursa, arrest in the development of the primitive heart tube, and, in particular, arrest in the development of the dorsal and ventral mesenteries so that the structures derived from the gut develop in situ in a symmetrical manner instead of early evidencing the asymmetry that appears to be initiated by a break in the ventral mesentery. A common mesentery and varying degrees of malrotation of the viscera ensue. A simple persistence of symmetry rather than a suppression of leftness as suggested by Putschar and Manion[92] would seem to be the basic disturbance, since the omental bursa that develops in the right dorsal mesogastrium opposite the primordium of the spleen has been reported absent in several of the more carefully documented cases; it seems possible that its absence has been overlooked in other instances.

It seems unlikely that resulting abnormal blood currents influence the development of the heart (Forgacs[105]), since symmetry and partial situs inversus of the abdominal viscera can occur with a normal heart, and a malformed heart, in the absence of anomalies of the abdominal viscera other than agenesis of the spleen. In such instances the lethal factor would seem to be of only moderate severity. The heart may be profoundly affected, resulting in a primitive structure consisting of a single atrium, single ventricle, and truncus arteriosus as in the authors' case 5; not affected at all, as in the case cited by Ivemark;[46] or affected so that portions of it proceed to develop normally while other portions are arrested, as in case 3. It seems most likely that it is the initial degree of severity of the lethal factor that determines the outcome rather than an arrest of the atrioventricular region resulting in trunco-conal abnormalities as suggested by Ivemark, since an atrioventricularis communis without splenic agenesis occurs more often without than with an anomaly of the trunco-conal region.

This factor would seem to affect specifically the germinal bed of the mesoblastic surface of the coelom. The structures derived from the gut, although symmetrical and malposed, including instances where the dorsal pancreas develops separately from the ventral pancreas, rarely show arrest in their development.[46, 57, 66, 83, 88, 89]

The timing of the operation of this factor at 24 to 28 days raises the question whether it is a by-product of a faulty or abortive ovulation released into the blood stream at the time ovulation would have taken place had a pregnancy not occurred. From a practical standpoint, a study of pregnant women 2 weeks after their first missed menstrual period might result in a discovery of this factor and ultimately lead to preventive measures.

Summary

The literature on splenic agenesis associated with congenital malformations of the heart has been reviewed and 5 additional cases have been reported. The current theories of etiology have been discussed. Certain postulations concerning the probable explanation for the combination of lesions found in this syndrome, have been advanced.

Acknowledgment

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Addendum

Since the preparation of this paper 18 additional cases of congenital malformations of the heart associated with splenic agenesis have been reported[105–115] and 1 additional case of splenic agenesis in an infant without a cardiac malformation.[116]

Summario in Interlingua

Es presentate un revista del litteratura relative a agenese splenic occurrente in association con congenite malformationes del corde. Es reportate 5 casos additional. Le currente theorias etiologic es discutite. Certe postulationes es facite concernente le explication probabile del occurrentia combinate del lesiones que es incontrate in iste syndrome.

REFERENCES

1. Pohlius, J. C.: Casum Anatomicum de Defectu Lienis Sistit et de Liene. In Genere Quaedam Disserit Simulque Collegium Disputatorium Publicum Indicit. Lipsiae, 1740, p. 3.
2. Schenkius a Grafenberg: Observationes Medicae Rarae Novae. Frankfurt, E. Paltheniana, Sumtibus Ionae Rhodii, Vol. 1, Lib. III, Sectio posterior, 1600, Obs. 7, p. 749.
3. Hollerius, J.: Cited by Schenkius a Grafenberg: Observationes Medicae Rarae Novae. Frankfurt, E. Paltheniana, Sumtibus Ionae Rhodii, Vol. 1, Lib. III, Sectio posterior, 1600, p. 787.
4. Jünisch.: Mangel der Milz. Misc. Ac. nat. cur. Dec. 1, ann. 3, 1684, p. 491. Cited by Heusinger.[10]
5. Jauch.: 1740. Cited by Putschar.[26]
6. Göller.: Misc. ac. nat. cur. Dec. II ann. 2, 1683, p. 314. Cited by Heusinger.[10]
7. Lemery.: Fehlen der Milz. Memoirs de l'Academie des Sciences, 1704, p. 21. Cited by Heusinger.[10]
8. Martin, M. G.: Observation d'une déviation organique de l'éstomac, d'une anomalie dans la situation, dans la configuration du coeur et des vaisseaux qui en partent ou qui s'y rendent. Bull. Soc. Anat. de Paris, **1**: 40, 1826.
9. Breschet, G.: Mémoire sur l'ectopie de l'appareil de la circulation et particulièrement sur celle du coeur. Répert. gén. d'anat. et physiol. path. **2**: 1, 1826.
10. Heusinger, C. F.: Die Hemmungsbildung der Milz, Zusammengestellt. Deutsches Arch. ges. Physiol. **6**: 17, 1820.
11. Bujalski, E.: Situs inversus, Agenesie der Milz. St. Petersburg, 1829.
12. Robert, H. L. F.: Hemmungsbildung des Magens, Mangel der Milz und des Netzes. Arch. f. Anat. Physiol. u. wissenschr. Med. 1842, p. 57.
13. Lebby, R.: Case of absence of the spleen. South. J. M. & Pharm. **1**: 481, 1846.
14. Hoffman, E. V.: Lehrbuch der Gerichtlichen Medizin. Ed. 4. Wien u. Leipzig, Urban and Schwarzenberg, 1887, p. 740.
15. Ramsay, H. A.: Gastroenteritis of twelve months' duration, exhibiting in autopsy an entire absence of the spleen and calcareous deposits in both lungs. Charleston M. J. & Rev. **5**: 728, 1850.
16. Birch-Hirschfeld, F. D.: Defect der Milz bei einem Neugeborenen. Arch. d. Heilk. **12**: 190, 1871.
17. Koch and Wachsmuth: Fehlen der Milz. Berlin Klin. Wchnschr. **16**: 81, 1879.
18. Jelenski: Fehlen der Milz. Berlin Klin. Wchnschr. **17**: 704, 1880.
19. Toldt, C.: Die Darmnekröse und Netze im gesetzmässigen und gesetzwidrigen Zustand. Denkschr. d. kais. Akad. d. Wiss. Wien. Math-nat. Kl. **56**, 1, 1889.
20. Olaechea, G. M.: Caso raro de ausencia del bazo. Crón. Mèd., Lima **13**: 147, 1896.
21. Sternberg, C.: Ein Fall von Agenesie der Milz. Arch. path. Anat. **173**: 571, 1903.
22. Glinski, L. K.: Wrodzony brak sledziony. Przegl. lek. Krakow **45**: 707, 1906.
23. Grusdeff, S. S.: Vorzhdennoye otsutstvije selezyonki. (Agenesia lienis, aliena.). Med. pribav. k. morsku. Sbornikv, St. Petersburg, 1908, p. 248.
24. Riches, R. G.: A case of congenital absence of the spleen. J. Ment. Sc. **60**: 630, 1914.
25. Titoff, I. T.: Agenesia lienis. Arch. path. Anat. **255**: 580, 1925.
26. Putschar, W. G. J.: Die Entwicklungstörungen der Milz. *In* Schwalbe-Gruber

Missbildungen des Menschen und der Tiere. Jena, G. Fischer, vol. 3, 1934, p. 759.

27. Nelson, R. L. and Venable, D. R.: Report of a case of congenital absence of the spleen and chronic amniotic fluid pneumonia. J. Lab. & Clin. Med. **26**: 772, 1941.
28. Charache, H.: Lymphosarcomatosis and congenital absence of spleen. New York State J. Med. **42**: 1363, 1942.
29. Caveda, C. P.: Neumonía amniótica; ausencia congénita de baso y situs inversus partialis. Rev. méd.-quir. de Oriente **6**: 22, 1945.
30. Germinale, T.: Un caso di assenza congenita della milza. Pathologica **41**: 96, 1949.
31. Millar, J. and Garrow, D. G.: Abnormal position of the aortic arch and absent spleen. Canad. M. A. J. **68**: 488, 1953.
32. Myerson, R. M. and Koelle, W. A.: Congenital absence of the spleen in an adult. Report of a case associated with recurrent Waterhouse-Friderichsen syndrome. New England J. Med. **254**: 1131, 1956.
33. Willi, H. and Gasser, C.: The clinical diagnosis of the triad spleen agenesis, defects of the heart and vessels and situs inversus. Études Néonatales **4**: 25, 1955.
34. Marrigues.: Une lettre à Morand. Mem. de mathém. présentés à l'acad. roy. des sciences, t. 4, p. 125 et 129. Daniel, col. op. med., Leipzig, 1776, p. 276. Cited by Breschet.[8]
35. Meinhard.: Medizine Zeitung, Rutzlands. 1844, p. 167.
36. Hodenpyl, E.: A case of apparent absence of the spleen with general compensatory lymphatic hyperplasia. Med. Record New York. **54**: 695, 1898.
37. Sachs, J. J.: Cited by Hodenpyl.[36]
38. Peterman, M. G.: Congenital absence of the spleen and left kidney. J. A. M. A. **99**: 1252, 1932.
39. Panà, C.: Alienia congenita: Reazioni secondarie vicariante nell'apparato emo-linfatico. Hematologica Arch. **15**: 469, 1934.
40. Otto, A. W.: Handbuch der Pathologischen Anatomie des Menschen und der Tiere. Breslau, C. F. Barth, 1814, p. 310.
41. Baker, G. H.: Absence of the spleen. Anatomical notes and queries. Number 41. J. Anat. & Physiol. **33**: 504, 1899.
42. Kohlhaas.: Völliger Mangel der Milz. Med. Cor.-Bl. d. Württemberg ärztl. Ver. **74**: 732, 1904.
43. Rose, F. G.: Absence of the spleen. Brit. M. J. **1**: 591, 1918.
44. Grewal, R. S.: A case of congenital absence of the spleen. Indian M. Gaz. **57**: 461, 1922.
45. Varma, T. N.: Congenital absence of the spleen. Indian J. Med. **3**: 157, 1922.
46. Ivemark, B. I.: Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood. An analysis of the heart malformation in the splenic agenesis syndrome with fourteen new cases. Acta paediat. **44**: 1. Suppl. 104, 1955.
47. Valleix, M.: Transposition irrégulière des organes. Bull. Soc. Anat. de Paris **9**: 264, 1834.
48. Wiener, Gebär and Findelhaus: 1857. Cited by Toldt.[19]
49. Arnold, J.: Ein Fall von Cor triloculare biatriatum, Communication der Lungenvenen mit der Pfortader und Mangel der Milz. Arch. path. Anat. **42**: 449, 1868.
50. Rokitansky, C. F. v.: Die Defecte der Scheidewände des Herzens. Wien, Braumüller, 1875.
51. Epstein, A.: Beitrag zu den Bildungsfehlern des Herzen. II. Defect des Kammerseptums; partieller Defect des Vorhofseptums; Einmündung der beiderseitigen Lungenvenen in die obere Hohlvene und das rechte Herz; Einmündung eines Lebervenenstammes in das linke Herz; rechsläufige Aorta; Mangel der Milz und des grossen Netzes; gemeinschaftliches Dünn- und Dickdarmgekröse, nebst anderen Abnormitäten. Ztschr. Heilk. **7**: 308, 1886.
52. Jonguenheim, cited by Schrötter.: Über angeborene Dextrocardia. Berl. Klin. Wchnschr. **24**: 448, 1887.
53. Kundrat, cited by Schrötter.: Über angeborene Dextrocardia. Berl. Klin. Wchnschr. **24**: 448, 1887.
54. Kundrat.: Über die anatomischen Verhaltnisse bei Transpositio cordis. Berl. d. k. k. Gesellsch. der Aerzte in Wien, med. Bl. **11**: 135, 240, 301, 1888.
55. Geipel, P. V.: Ein Beitrag zur Lehre des Situs transversus. Festschrift zur Feier des fünfzigjahrigen Bestandes des Stadtkrankenhauses zu Dresden-Friedrichstadt, herausgegeben vom Rathe zu Dresden. W. Baensch Verlag, Dresden, 1899, pt. 2, p. 373.
56. Lawrence, T. W. P. and Nabarro, D.: A case of congenital malformation of the heart, with abnormalities of abdominal viscera: absence of spleen, absence of hepatic section of inferior vena cava. J. Anat. Physiol. **36**: 63, 1901.
57. Krausse, O.: Ein Beitrag zur Lehre von den kongenitalen Herzfehlern und ihrer Koinzidenz mit anderen Missbildungen (Alienie). Jahrb. Kinderh. **62**: 35, 1905.
58. Gardère.: Maladie bleue; malformation congénitale du coeur. Lyon Méd. **110**: 897, 1908.

59. Mönckeberg, J. G.: Beitrag zur Entwicklungsgeschichte des Atrioventrikularsystems und zu seinem Verhalten bei schwerer Missbildungen des Herzens. Zentralbl. Herz - u. Gefässkrankh. **7**: 273, 1915.
60. Bossert, O. and Leichtentritt, B.: Die Bedeutung der bakteriologischen Blutuntersuchung für die Pathologie des Säuglings. Jahrb. Kinderh. **92**: 152, 1920.
61. McLean, S. and Craig, H. R.: Congenital absence of the spleen. Am. J. M. Sc. **164**: 703, 1922.
62. Pernkopf, E.: Der partielle Situs inversus der Eingeweide beim Menschen. Gedanken zum Problem der Asymmetrie und zum Phanomen der Inversion. Ztschr. Anat. u. Entwcklngsgesch. **79**: 577, 1926.
63. Garvin, J. A.: Dextrocardia with pulmonary artery arising from the aorta. Am. J. Dis. Child. **34**: 133, 1927.
64. Hu, C. H.: Congenital malformation of the heart with anomalous insertion of pulmonary veins, absence of spleen, situs inversus of abdominal viscera and other developmental errors. Am. J. Path. **5**: 389, 1929.
65. Feldman, B. A.: Ein Fall von Situs viscerum inversus partialis, kombiniert mit anderen Entwicklungsanomalien. Jahrb. Kinderh. **129**: 221, 1930.
66. Kimura, H.: On double penis and its complications (atresia ani simplex, cor biloculare and absence of the spleen, etc.). Japan M. World **10**: 63, 1930.
67. Shapiro, P. F.: Detorsion defects in congenital cardiac anomalies. Report of three cases, with an analysis of the mechanism of their formation. Arch. Path. **9**: 54, 1930.
68. Behr, E.: Een Geval van Agense van de Milt. Nederl. tijdschr. v. geneesk. **76**, 1490, 1932.
69. Kugel, M. S.: Congenital heart disease. Cor biloculare. Am. Heart J. **8**: 280, 1932.
70. Gerstenberger, H.: Ein Fall von Situs inversus totalis mit multiplen Missbildungen des Herzens und der Gefässe. Frankfurt Ztschr. Path. **52**: 243, 1938.
71. Fueter, A.: Über einen Fall seltener, komplizierter Herzmissbildung. Gegenbaur's Morphol. Jahrb. **81**: 245, 1938.
72. Taussig, H. B.: Cardiovascular anomalies. A single ventriele with a diminutive outlet chamber. J. Tech. Methods **19**: 124, 1939.
73. Lightner, C. M.: An unusual congenital malformation of the heart: cor biloculare with ostium atrioventriculare commune, pulmonary atresia, displacement of right pulmonary veins, and associated somatic defects. J. Tech. Methods **19**: 148, 1939.
74. Durie, B. and Wyndham, N. R.: Description of two human specimens with congenital absence of the spleen, abnormal arrangements of the great vessels, abnormal cardiac cavities and other congenital defects. M. J. Australia **2**: 174, 1942.
75. Rossman, J. I.: Cor biloculare with transposition of the great cardiac vessels and atresia of the pulmonary artery: Phylogenetic and ontogenetic interpretation. Am. J. Clin. Path. **12**: 534, 1942.
76. Young, M. O.: Common trunk of pulmonary veins tributary to the portal vein, with a multiple cardiac anomaly. Arch. Path. **44**: 169, 1947.
77. Weinberg, T. and Kolson, J. W.: Drainage of the pulmonary veins into portal vein in association with cardiac defects and partial situs inversus. J. Tech. Methods **30**: 68, 1949.
78. Conn, J. J., Clark, T. E. and Kissane, R. W.: Cor biloculare: Report of four cases. Am. J. Med. **8**: 180, 1950.
79. Leikin, S. L.: Partial situs inversus with levocardia. Clin. Proc. Child. Hosp., Washington, D. C., **7**: 236, 1951.
80. Jaccard, R.: À propos de deux cas de transposition complète des gros vaisseaux. Helvet. paediat. acta **6**: 225, 1951.
81. Gasser, C. and Willi, H.: Spontane Innenkörperbildung bei Milzagenesie. Helvet. paediat. acta **7**: 369, 1952.
82. Lüdin, M.: Ein Fall von Cor biloculare mit Einmundung der Lungenvenen in die Leberpforte. Beitr. z. path. Anat. u. z. allg. Path. **112**: 380, 1952.
83. Polhemus, D. W. and Schafer, W. B.: Congenital absence of the spleen; syndrome with atrioventricularis and situs inversus; case reports and review of the literature. Pediatries **9**: 696, 1952.
84. Adler, N. N. and Van Slyke, E. J.: Congenital absence of the spleen. J. Pediat. **42**: 471, 1953.
85. Boggs, J. D. and Reed, W.: Congenital absence of the spleen. Quart. Bull. Northwestern Univ. M. School **27**: 289, 1953.
86. Campbell, M., Reynolds, G. and Trounce, J. R.: Six cases of single ventriele with pulmonary stenosis. Guy's Hosp. Rep. **102**: 99, 1953.
87. Campbell, M. and Forgacs, P.: Laevocardia with transposition of the abdominal viscera. Brit. Heart J. **15**: 401, 1953.
88. Baumann, J.: Agenesie der Milz, Herz - und Gefässmissbildungen und Situs inversus partialis; ein charakteristischer Symptomenkomplex. Helvet. paediat. acta **9**: 199, 1954.
89. Putschar, W. G. J.: Über angeborenen Milzmangel (drei Fälle und Ubersicht der

neuen Literatur). Zentralbl. allg. Path. u. path. Anat. **92**: 390, 1954.

90. Bush, J. A. and Ainger, L. E.: Congenital absence of the spleen with congenital heart disease. Report of a case with antemortem diagnosis on the basis of hematologic morphology. Pediatrics **15**: 93, 1955.
91. Polhemus, D. W. and Schafer, W. B.: Congenital absence of the spleen. Pediatrics **16**: 495, 1955.
92. Putschar, W. G. J. and Manion, W. C.: Congenital absence of the spleen and associated anomalies. Am. J. Clin. Path. **26**: 429, 1956.
93. Streeter, G. L.: Developmental Horizons in Human Embryos. Description of age groups XV, XVI, XVII and XVIII, being the third issue of a survey of the Carnegie Collection. Carnegie Contributions to Embryology **32**: No. 211, 1948, p. 134.
94. Wedum, B. G.: The Development of the Heart and Great Vessels. Exhibit based on the work of C. L. Davis, G. L. Streeter, and O. O. Heard, shown at the International Cardiac Congress, Washington, D. C., September, 1954.
95. Streeter, G. L.: Developmental Horizons in Human Embryos 11-23. Collected papers from the Contributions to Embryology. Published by the Carnegie Institution of Washington. Embryology reprint, Vol. 2, 1951.
96. Hamilton, W. J., Boyd, J. D. and Mossman, H. W.: Human Embryology. Cambridge, Heffer and Sons, 1952, p. 162.
97. Arey, L. B.: Developmental Anatomy. Ed. 4. Philadelphia, W. B. Saunders Co., 1943, p. 216.
98. Auër, J.: The development of the human pulmonary vein and its major variations. Anat. Rec. **101**: 581, 1948.
99. Edwards, J. E.: Pathologic and developmental considerations in anomalous pulmonary venous connection. Proc. Staff Meet., Mayo Clin. **28**: 441, 1953.
100. Geipel, P. v.: Weitere Beitrage zum Situs transversus und zur Lehre von den Transpositionen der grossen Gefasse des Herzens. Arch. Kinderh. **35**: 112, 1903.
101. Töndury, G.: Über Situs inversus partialis beim Menschen. Ztschr. f. Anat. u. Entwcklngsgesch. **106**: 648, 1936.
102. Torgesen, J.: Genetic factors in visceral asymmetry and in the development and pathologic changes of lungs, heart and abdominal organs. Arch. Path. **47**: 566, 1949.
103. —: Situs inversus, asymmetry, and twinning. Am. J. Human Genetics **2**: 361, 1950
104. —: The developmental anatomy of the hear and the etiology of congenital heart disease Acta radiol. **33**: 131, 1950.
105. Forgacs, P.: Congenital heart disease wit isolated inversion of the abdominal viscera Brit. Heart J. **9**: 27, 1946.
106. Doerr, W.: Zur Transposition der Herz schlagadern. Ein kritischer Beitrag zu Lehre der Transpositionen. Arch. path Anat. **303**: 168, 1938.
107. —: Über Missbildungen des menschliche Herzens mit besonderer Berucksichtigun von Bulbus und Truncus (Truncus arteriosu comm. persistens, Transpositionen un Stenosen). Arch. path, Anat. **310**: 304. 1943.
108. Aguilar, M. J., Stephens, H. B. and Crane J. T.: Syndrome of congenital absence o the spleen with associated cardiovascular and gastroenteric anomalies. Circulation **14**: 520. 1956.
109. Nihoyannopoulos, J., Zannos, L., Oeconomou-Mavrou, C. and Statherou, E.: Report of a case with congenital absence of the spleen and laevocardia. J. Clin. Path. **9**: 323, 1956.
110. Cyanosis from birth. *In* Case Reports of the Children's Memorial Hospital, Chicago **14**: 3915, 1956.
111. Plowman, D. E. M.: Congenital absence of the spleen associated with cardiac abnormalities. Brit. M. J. **1**: 147, 1957.
112. Towers, B. and Middleton, H.: Congenital absence of the spleen associated with malformations of the heart and transposition of the viscera. J. Path. & Bact. **72**: 553, 1956.
113. Leadbeater, N. A. G.: Congenital absence of spleen. Brit. M. J. **1**: 342, 1957.
114. Levy, D.: Congenital malformation of the heart and the great vessels associated with congenital absence of the spleen. Arch. Dis. Child. **32**: 131, 1957.
115. Lyons, W. S., Hanlon, D. G., Helmholz, H. R., Jr., DuShane, J. W. and Edwards, J. E.: Cardiac Clinics. CXLVIII. Congenital cardiac disease and asplenia. Report of seven cases. Proc. Staff Meet., Mayo Clinic **32**: 277, 1957.
116. Murphy, J. W. and Mitchell, W. A.: Congenital absence of the spleen. Pediatrics **20**: 253, 1957.

The Ballistocardiogram in Overweight Young Adults

By SAMUEL STERN, M.D.

(With the technical assistance of Miss Aja Lipavsky)

The ability to record the mechanical function of the heart is the principal value of the ballistocardiogram. In young healthy individuals the ballistocardiogram is consistently normal. Since overweight is apparently an important factor in the development of degenerative heart diseases, a study was undertaken to correlate excess weight in otherwise healthy young students with their respective ballistocardiograms, obtained on a direct-body ballistocardiograph.

THE clinical value of ballistocardiography is still limited. There is still considerable discussion as to what constitutes the normal ballistocardiogram,[1] and what are the pathognomonic patterns for specific diseases.[2] There are, however, some general values based on studies with large groups of patients, followed for long periods, that are well documented. Several authors[3-5] have described the rather frequent occurrence of markedly abnormal tracings among older people. A definitely abnormal tracing, on the other hand, among healthy young adults is an unusual occurrence.

In general one might say that in an elderly patient a normal ballistocardiogram is more helpful to the clinician than is an abnormal one. An abnormal pattern in a young person, however, warrants careful search for cardiac disease, and though no obvious heart disease may be present, the clinician has to be concerned with the prognostic significance of the abnormal tracing.[6, 7]

In this paper a ballistocardiographic study is reported in a group of young adults who, according to the conventional diagnostic tools and clinical criteria, had no cardiovascular disease. The correlation between their ballistocardiograms and physical characteristics is elaborated.

MATERIALS AND METHODS

One hundred and fifty young adults, 100 females from the nursing school attached to our hospital, and 50 males from the University of Cincinnati Medical School were studied. Each subject had undergone a complete physical examination, with particular reference to the cardiovascular system, and was found to be in good health. The upper age limit of this group was 25 years, and a blood pressure not exceeding 135/95 mm. Hg was a prerequisite. An x-ray film of the chest and an electrocardiogram were reported as normal on every subject.

The ballistocardiogram was obtained according to Dock's direct-body method.[8] A commercial Pordy dual ballistocardiograph [9] was used, with a special sturdy wooden table serving as support. The records were drawn over the velocity (electromagnetic) channel, mainly because of the respiratory interference that is more marked over the displacement (photoelectric) channel. The subjects were asked to lie on the bare table with their legs at 45° external rotation. This was found to be the most relaxed position under the circumstances. The crossbar was placed over the ankles, so that the magnet was directly in front of the coils. A distance of a quarter inch was maintained between the magnet and the main body of the machine in the vertical and horizontal planes. The tracings were recorded with a "Simpli-Scribe" (Cambridge) direct-writer electrocardiograph.

Three strips were obtained on each subject: the first during quiet respiration, the second during sustained full inspiration, and the third during sustained full expiration. The ballistocardiograms were interpreted and classified according to Dock's[10] criteria and categories. The minor modifications of Brotmacher[1] were applied. Weights were assessed in accordance with the height, age, frame, and weight charts.[11]

RESULTS

Of a group of 150 records, 23 were found to be abnormal. When classified, 12 of the abnormal tracings were in grade 1, 7 in grade 2, 2 in grade 3, and 2 in grade 4.

When the students were classified according to their weights, 23 were found to be at least 20 pounds overweight, and 21 of the abnormal tracings were in this group. One abnormal

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TABLE 1.—*Excess Weight Correlated to Ballistocardiographic Abnormality in Young Students*

Number of students	Over weight (lbs.)	Grades				
		0	1	2	3	4
2	0 - 20	—	2	—	—	—
15	20 - 40	2	10	3	—	—
3	40 - 60	—	—	2	1	—
1	60 - 80	—	—	1	—	—
4	80 <	—	—	1	1	2

record was obtained from a normal-weight adult and 1 from a student 6 pounds overweight. Two adults of the overweight group displayed normal patterns.

When the amount of excess weight was correlated with the degree of abnormality in the ballistocardiogram (table 1), the most severe ballistocardiographic abnormalities appeared in the more severely obese students. Thus the data suggest linear correlation between the amount of excess weight and the degree of ballistocardiographic abnormality.

During normal respiratory cycles the inspiratory complexes of the ballistocardiogram were taller than they were during the expiratory phases, as observed by previous investigators.[12] However, in most of our records obtained during full and sustained expiration, the complexes were of higher amplitude than those recorded during full and sustained inspiration or during normal respiratory cycles (fig. 1). We cannot explain this phenomenon, but venture to suggest that the hyperinflated lungs increased the damping factor, while the reverse occurred with the deflated lungs.

DISCUSSION

From a theoretical point of view the ballistocardiogram seems to be superior in clinical value to the electrocardiogram. Starr has described the electrocardiogram as the spark for the engine while the actual explosion is being recorded by the ballistocardiogram. The clinician, whose primary interest lies with the mechanical efficiency of the heart, may obtain information from the ballistocardiogram. Yet,

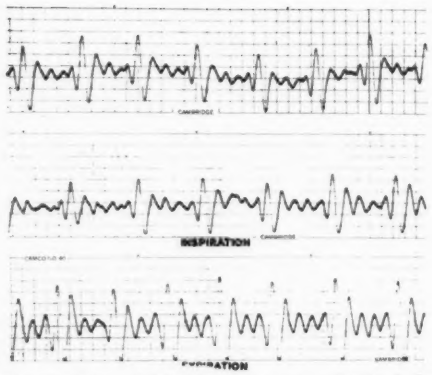

FIG. 1. Normal ballistocardiogram, obtained from a young healthy student of normal weight.

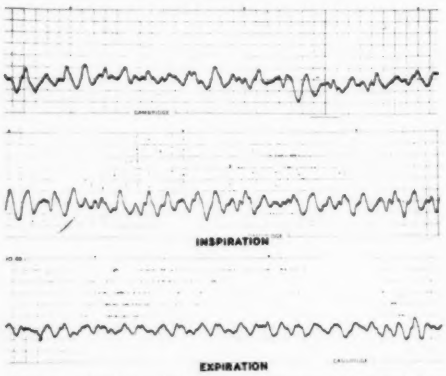

FIG. 2. Grade 4 ballistocardiogram, obtained from a young student 90 pounds overweight.

from a practical standpoint the ballistocardiogram is rarely used and only on a selective basis. The reasons for this are, first, the relatively young age of ballistocardiography, but second, and mainly, the higher dependency of the mechanical force, as compared to the electric force, on the medium through which it travels. While cardiac function may be normal, peripheral tissue changes with age may markedly modify the spreading vibrations.[13] The main handicap and problem of ballistocardiography seem to be the differentiation between its cardiac and extracardiac components.

In young adults this problem does not exist, yet 23 of our group demonstrated abnormal patterns. Twenty-one of these 23 abnormal records were in young adults with at least 20 pounds excess weight. Moreover, the degree

of obesity was directly proportional to the grade of ballistocardiographic abnormality. One might assume that this is another example of extracardiac factors interfering with the normal propagation of the forces originating within the normal heart. If, however, one accepts Starr's and Braunstein's evidence concerning the prognostic value of the abnormal ballistocardiogram, then the results of this paper might serve as circumstantial evidence that early degenerative heart disease is in fact beginning in obese young adults with abnormal ballistocardiograms. Undoubtedly, as with many other problems in ballistocardiography, further follow-up studies will settle this problem. Ballistocardiograms on the overweight patient should, however, be interpreted with reservation. Recent communication with Dr. Braunstein revealed that he has had similar experience with obese patients of the older age group. It is his practice to withhold a definite interpretation in such cases.

The results of this paper reaffirm the importance of the ballistocardiogram in young adults. Excluding the overweight, only 1 of the 150 healthy students displayed an abnormal pattern, and this was of grade 1, abnormality.

Summary

A group of young adults under strict criteria for cardiovascular normality has been studied by means of the direct-body ballistocardiograph. The correlation between their weight and ballistocardiographic pattern has been evaluated. It was found that overweight young adults had abnormal ballistocardiograms. This abnormality increased with the amount of obesity. The significance of these findings and their practical application is discussed.

Acknowledgment

We wish to thank Drs. F. Donath, T. Levin, J. R. Braunstein, R. Shabatai, and S. Polasky for reviewing this paper.

Summario in Interlingua

Un gruppo de juvene adultos, seligite secundo stricte criterios de normalitate cardiovascular, esseva studiate per medio de ballistocardiographia directe. Le correlation inter le pesos corporee del subjectos e le configuration de lor ballistocardiogrammas esseva evalutate. Esseva constatate que juvene adultos con excesso de peso habeva ballistocardiogrammas anormal. Le anormalitate se accentuava con augmentos del obesitate. Le signification de iste constatationes e lor application practic es discutite.

REFERENCES

1. Brotmacher, L.: The normal ballistocardiogram. Brit. Heart J. **18**: 145, 1956.
2. Yuceoglu, Y. Z., Pordy, L., Chesky, K. and Donoso, E.: The ballistocardiogram in coarctation of the aorta. Am. Heart J. **53**: 446, 1957.
3. Starr, I. and Mayock, R. L.: On the significance of abnormal forms of the ballistocardiogram. Am. J. M. Sc. **215**: 631, 1948.
4. Pordy, L., Taymor, R. C., Moser, M., Chesky, K. and Master, A. M.: Clinical evaluation of the ballistocardiogram. Am. Heart J. **42**: 321, 1951.
5. Scarborough, W. R., Mason, R. E., Davis, F. W., Singewald, M. L., Baker, B. M. and Lore, S. A.: A ballistocardiographic and electrocardiographic study of 328 patients with coronary artery disease; Comparison with results from a similar study of apparently normal persons. Am. Heart J. **44**: 645, 1952.
6. Starr, I.: On the later development of heart disease in apparently healthy persons with abnormal ballistocardiograms. Eight to ten-year after-histories of 90 persons over 40 years of age. Am. J. M. Sc. **214**: 233, 1947.
7. Braunstein, J. R.: The Ballistocardiogram—Dynamic Record of the Heart Beat. Springfield, Ill., Charles C Thomas, 1953.
8. Dock, W. and Taubman, F.: Some technics for recording the ballistocardiogram directly from the body. Am. J. Med. **7**: 751, 1949.
9. Pordy, L., Chesky, K., Master, A. M., Taymor, R. and Moser, M.: The dual displacement and velocity ballistocardiograph apparatus. Am. Heart J. **44**: 248, 1952.
10. Dock, W., Mandelbaum, H. and Mandelbaum, R. A.: Ballistocardiography. St. Louis, The C. V. Mosby Co., 1953.
11. Sunderman, F. W. and Boener, F.: Normal Values in Clinical Medicine. Philadelphia, W. B. Saunders Co., 1949, and Metropolitan Life Insurance Co. Weight Charts.
12. Starr, I. and Friedland, C. K.: On the cause of respiratory variation of the ballistocardiogram with a note on sinus arrhythmia. J. Clin. Invest. **25**: 53, 1946.
13. Jacobs, H. D.: Ballistocardiographic observations. Brit. Heart J. **16**: 79, 1954.

The Atrial Coronary Arteries in Man

By THOMAS N. JAMES, M.D., AND GEORGE E. BURCH, M.D.

An anatomic study of the atrial coronary arteries in 43 fresh normal human hearts is described. The implications of the findings are discussed for clinical problems facing the cardiologist and the cardiovascular surgeon.

THE arterial supply of the atria has received little attention, and the anatomic descriptions available are conflicting. Textbooks of anatomy[1] dismiss the arterial supply of the atria with a sentence stating that they receive arterial branches from the coronary artery of their respective sides.

Interest in atrial circulation[2] increased slightly with discovery of the sinoatrial and atrioventricular nodes. The most significant studies in human hearts were those of Keith and Flack,[3] Spalteholz,[4] Crainicianu,[5] and Gross.[6] Several excellent studies of the blood supply to the canine cardiac atria have been reported in recent years;[2, 7-10] however, these observations fail to clarify the situation for man.

A knowledge of circulation in the atria is of importance, especially with respect to the normal cardiac pacemaker and atrial portion of the conduction system. The arterial circulation may influence the function of these structures, particularly as related to cardiac arrhythmias. Furthermore, recent interest in cardiac surgery makes detailed knowledge of the atrial anatomy of greater importance. To clarify some of the conflicting descriptions of the atrial coronary arteries 43 human hearts were studied.

METHODS

All methods for studying the coronary arteries have shortcomings. Principally, 3 methods have been employed, any of which may be combined with classic dissection. The first consists of injection of the coronary vessels with colored opaque solutions, followed by dehydration of the specimen in alcohol and subsequent clearing with various oils.[4] This procedure preserves the entire heart and permits a study of the relationships of the coronary vessels to the other structures. Unfortunately only the superficial coronary vessels are adequately displayed and the interatrial or interventricular septa are not shown.

The second method consists of injecting radiopaque substances into the coronary arteries and then obtaining planar and stereoscopic roentgenograms to reveal the arterial distribution. This was the method employed by Gross[6] and Schlesinger and his colleagues.[11, 12] This type of examination provides a permanent record of vascular distribution while preserving the heart specimen for other studies such as the pathology. Examination of the intact heart by this method is confused by the crossing of depicted vessels, whereas preparations flattened ("unrolled") to avoid such overlapping distort the spatial orientation of cardiac structures.

The third method consists of injecting with a noncorroding substance and then digesting away the tissues. Many substances have been used for injection, the chief ones being celluloid,[13] low-melting-point metals,[14] and certain plastics.[15-17] This method provides an exact spatially oriented replica of the coronary vascular system, with distribution of the right and left coronary arteries being demonstrated separately by means of differently colored injection material. Additional casting of the great vessels and the cardiac chambers can assist in displaying the relationship of the vascular and nonvascular structures. To make possible associated histologic examinations, Baroldi, Mantero, and Scomazzoni[18] immersed their heart specimens in a 10 per cent formol bath after the plastic injection and obtained their sections of myocardium for microscopic study prior to corrosion.

After considering the various methods, we chose to use the injection and corrosion technic in our observations. Vinylite resin dissolved in acetone was used for injection and concentrated hydrochloric acid for corrosion, according to the method of Stern, Ranzenhofer and Liebow.[17]

The hearts of 32 males and 11 females, ages 12 to 81 years, were examined. The age distribution was similar in each decade except that only one was in the eighth and one in the ninth decade. These subjects died of noncardiac diseases or accidents.

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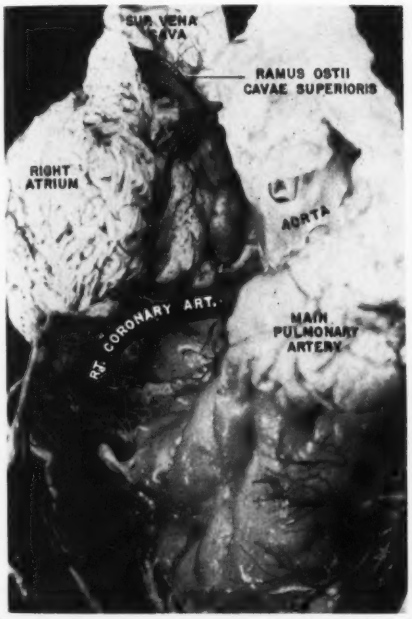


FIG. 1. Ramus ostii cavae superioris arising from the right coronary artery and terminating by encircling the base of the superior vena cava.

RESULTS

Arterial Supply of the Sinoatrial Node. The largest artery to the human cardiac atria supplies the region near the superior vena cava and sinoatrial node. Gross[6] named it the ramus ostii cavae superioris, regardless of its origin, while Spalteholz[4] arbitrarily designated the atrial arteries as anterior, intermediate, and posterior, depending upon their origin. Crainicianu[5] referred to this vessel as the Keith-Flack artery. Gross's term for this artery is specific and its use is recommended for the present.

In this series of 43 hearts, the ramus ostii cavae superioris was well demonstrated in 39 hearts, poorly in one heart and not at all in 3. The failure to demonstrate the vessel in the latter hearts was almost certainly technical in origin.

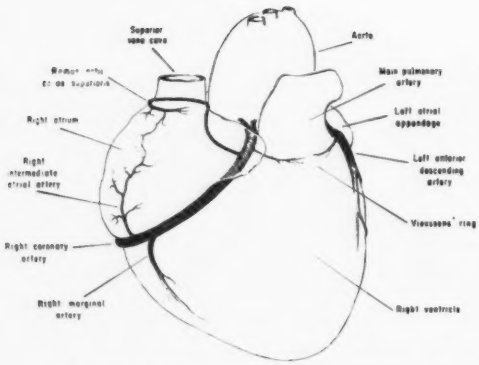
Although the ramus ostii cavae superioris varies considerably in its origin, its ultimate distribution appeared to be as constant as any other major artery of the body. It always terminated in the region of the orifice of the superior vena cava, and almost always did so by encircling that region.[3, 5, 6, 19]

Of the 39 hearts in which the ramus ostii cavae superioris was well demonstrated, it arose from the right coronary artery in 24 (61 per cent) and from the left in 15 (39 per cent). Gross found it to arise from the right coronary artery in 60 per cent and from the left in 40 per cent of his series of hearts.[6] Both in Gross's study and ours this vessel was never found to arise from both coronary arteries in the same heart. Communications with other atrial vessels did exist, however.

This atrial artery always arose from the first few centimeters of the right or left coronary artery, so that by Spalteholz's nomenclature it would be either the right or left anterior atrial artery. When it originated from the right coronary artery (figs. 1-3) it coursed cephalad and posteriorly along the body of the right atrium, behind the aorta, to reach the anterior interatrial groove. It ascended in this groove, distributed branches to both atrial walls, and terminated by encircling the orifice of the superior vena cava. The circle was complete or very nearly so, with some large branches descending from it toward the inferior vena cava, along the region of the tail or terminus of the sinoatrial node.

Grossly visible anastomoses that have been demonstrated are as follows: (1) With the terminal branches of the intermediate right atrial artery; and (2) with a small artery from the left circumflex coronary artery that coursed behind the two great vessels, and corresponds to one variation (26 per cent) of Kugel's arteria anastomotica auricularis magna.[20] Failure to demonstrate other communications should not be construed to imply that they do not exist.

When the ramus ostii cavae superioris arose from the left side (figs. 3-5) it most frequently originated from the left circumflex artery near its beginning but it also originated from the main left coronary trunk. From an origin on the left side it coursed cephalad along the body of the left atrium, behind the aorta, to reach the anterior interatrial groove. Its course and distribution were then similar



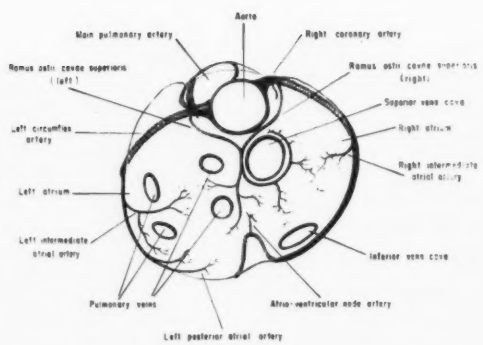


FIG. 2. *Left.* Schematic representation of the ramus ostii cavae superioris arising from the right coronary artery in the intact heart. The right intermediate atrial artery is shown communicating with the branches from the caval circle.

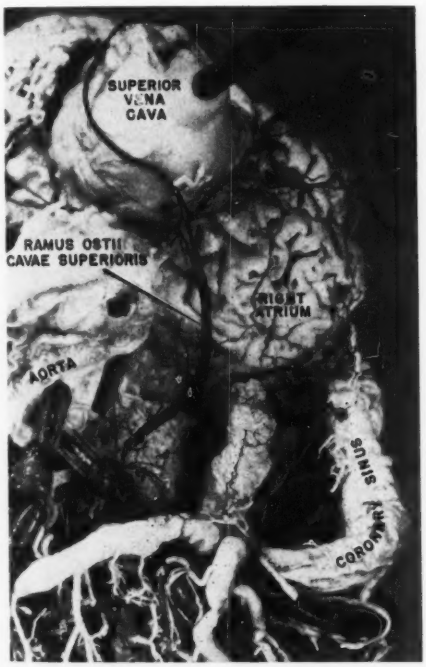
FIG. 3. *Right.* Schematic view of the top of the heart, showing the course of the ramus ostii cavae superioris from both a left and right origin; this simultaneous existence was not found to exist in the hearts studied, and is shown thus only as a means of illustration. The U turn of the right coronary artery and its branch to the atrioventricular node are shown.

to that described for the atrial artery that originated from the right coronary, terminating in a circle about the base of the superior vena cava. Grossly visible anastomoses that have been demonstrated for this artery are: (1) Over the body of the left atrium with the left intermediate atrial artery; and (2) in the interatrial septum with the posterior left and right atrial arteries, which corresponds to the major variation (66 per cent) of Kugel's arteria anastomotica auricularis magna.[20]

In 2 hearts the ramus ostii cavae superioris that arose from the left side had a course quite different from the typical one described above. Instead of going directly to the interatrial septum, the vessel traveled in the opposite direction (fig. 6), toward the margo obtusus, parallel but slightly above the atrioventricular sulcus. At the margo obtusus (where the left intermediate atrial artery usually arises) the vessel divided at right angles into 2 large branches. The one of these continued in essentially the course described above and distributed to the lateral and posterior walls of the left atrium. The other larger branches ascended over the top of the left atrium between the pulmonary veins, crossed the middle of the interatrial septal groove, and terminated in a circle about the base of the superior vena cava. Gross found the ramus ostii cavae superioris to originate occasionally as the left intermediate atrial artery. In the present study this type of origin was not found. It is possible that Gross was actually describing this unusual distribution, as his method could have resulted in misinterpretation of the origin of a large vessel seen near the margo obtusus.

Arterial Supply of the Atrioventricular Node. Though not as large as the ramus ostii cavae superioris, a constant artery (sometimes more than one) was found supplying the atrioventricular node region (figs. 7 and 8). It originated from the artery crossing the crus of the posterior wall of the heart, which was the right coronary artery in 35 hearts (83 per cent), the left coronary artery in 3 (7 per cent), and from both in 4 (10 per cent). The blood supply of this area was not satisfactorily demonstrated in one heart. Other investigators have also found a specific artery originating from the right coronary artery to supply the atrioventricular node.[3, 5, 6, 21] Gross applied the name of ramus septi fibrosi to this vessel.

This artery coursed anteriorly from its origin near the crus of the heart, traveling deep to the coronary sinus and rising cephalad to



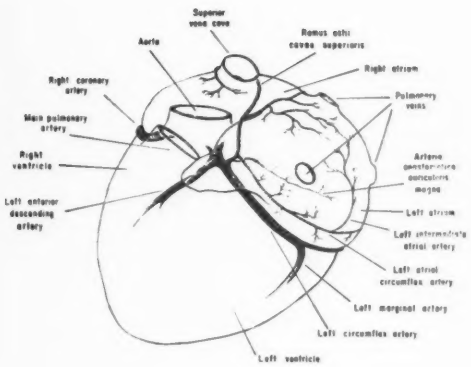


FIG. 4. *Left.* The ramus ostii cavae superioris as it arises from the left circumflex artery. Two cannulas are visible at the left coronary ostium because the left circumflex and left anterior descending arteries arose separately from the aorta in this heart.

FIG. 5. *Right.* Schematic drawing of the ramus ostii cavae superioris arising from the left circumflex artery. Note the long branch (left atrial circumflex artery) following the base of the left atrium, having arisen from the ramus ostii cavae superioris; in some hearts this branch arises from the left circumflex artery directly. Also shown is the arteria anastomotica auricularis magna (Kugel), which may arise from a left ramus ostii cavae superioris or directly from the left circumflex artery; it anastomoses posteriorly with the right or left coronary artery.

the base of the interatrial septum. It was usually straight and 2 to 3 cm. in length. The terminal branching was remarkable in that it always divided at an angle of 90° or greater from the main atrioventricular nodal artery. This right angle branching is also found in the perforating arteries that branch from the main vessels at the epicardial surface of the left ventricle, and again in the subendocar-

It was interesting to find that whether the artery to the atrioventricular node originated from either the right or left coronary artery, these main vessels made a sharp U-shaped turn under the posterior descending vein, with the atrioventricular nodal artery arising from the apex of the U (figs. 3, 8, and 9).

This U-shaped turn is possibly of considerable embryologic significance when examined in the light of Keith and Flack's study on the phylogeny of the atrioventricular node.[3] They noted that in lower animals, as well as in a 32-mm. human embryo, the node was situated on the epicardial surface, and that only when that portion of the myocardium invaginated to form the interatrial septum did the node become located inside the heart. Such an invagination could account for the peculiar course of the main coronary arteries at the point where they supply a branch to the atrioventricular node, as well as for the terminal right angle branching of this vessel.

Grossly demonstrated anastomoses of the atrioventricular nodal artery were as follows: (1) With perforating branches from the ante-

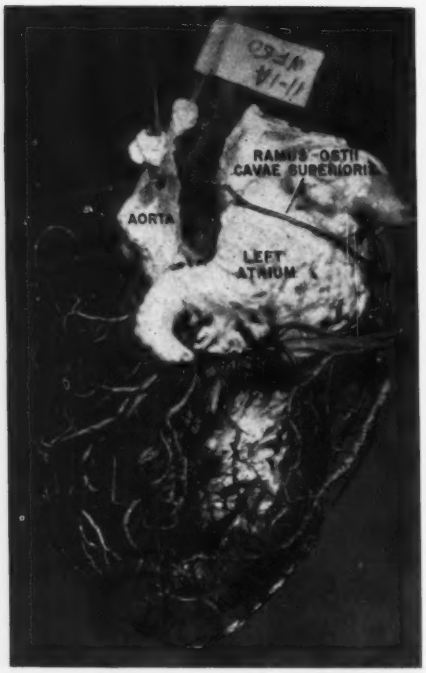


FIG. 6. An unusual course of the ramus ostii cavae superioris from the left coronary artery. A possible misinterpretation of this course is discussed in the text.

rior interatrial septum, which arose from the left circumflex artery, the left anterior descending artery, or the main right coronary artery (Kugel's arteria anastomotica auricularis magna); and (2) with right or left posterior atrial arteries which penetrated laterally into the posterior interatrial septum.

Other Arteries of the Atria. No other atrial arteries were found as commonly as these to the two nodes, nor were there other atrial arteries of size comparable to the ramus ostii cavae superioris. There are, however, several other arteries that are commonly seen. Because they are small, failure to demonstrate them consistently cannot be considered indicative of their absence. Because of this possible failure to demonstrate them in many of the 43 hearts, it would be misleading to indicate their percentile incidence.

Although Spalteholz's regional classification of atrial arteries and nomenclature is simple and appealing, this terminology may suggest that all hearts have anterior, intermediate, and posterior atrial arteries for the left and right atria. Our findings suggest that this is not always true, and would support the use of a different type of nomenclature.

Of these small and numerous atrial arteries, 2 groups were less variable than the others. The first of these was the group in the region of the margo acutus, similar to the location of Spalteholz's intermediate right atrial artery. There was usually at least one fairly large artery in this area. It ascended over the superior region of the right atrium to supply that portion of myocardium. It often anastomosed with branches from the artery that circled the base of the superior vena cava (figs. 2, 3, and 10).

The second group supplied the lateral wall of the left atrium, the site of Spalteholz's left intermediate atrial artery. When a vessel was large enough to demonstrate easily in this area, it often did not arise near the margo obtusus, but rather from the trunk of the ramus ostii cavae superioris shortly after it originated from the left circumflex coronary artery. Its course was then parallel to the left circumflex artery, but higher, along the base of the left atrium (fig. 5). It distributed branches to the atrial wall all along its course and terminated in the posterior portion of the left atrium. This vessel will be referred to as the left atrial circumflex artery. In 2 hearts, as described previously, it was actually the ramus ostii cavae superioris, supplying the sinoatrial node by first coursing over the superior surface of the left atrium.

The other small atrial arteries were only regional twigs. They may have important potentialities as collateral vessels. This is particularly true of those that perforate the anterior portion of the interatrial septum.[20] Small twigs in the region of the posterior atrial arteries described by Spalteholz may communicate with the main artery to the atrioventricular node. Tiny arteries were observed to encircle the left and right atrial appendages, but were more numerous around the left.

Veins and Venous Channels of the Atria. As the atrial chambers were cast, vessels were found to be filled directly from the lumen of

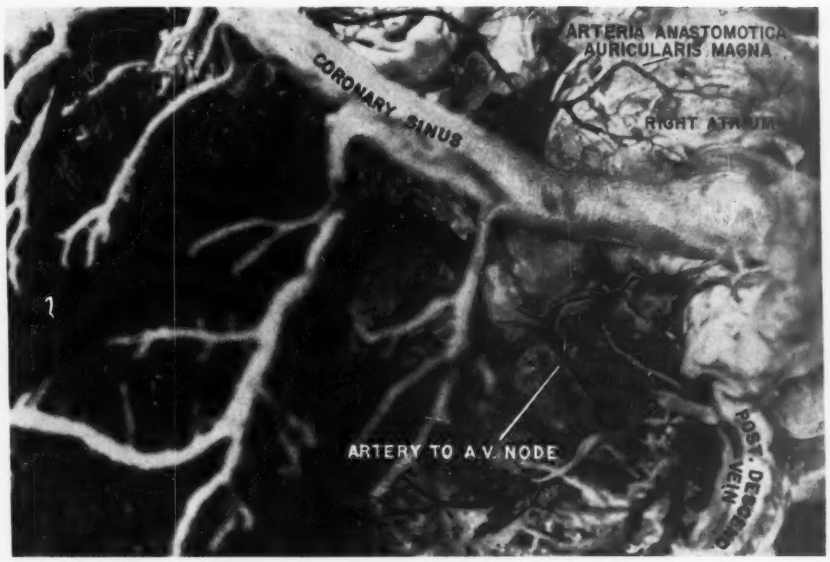


FIG. 7. The artery to the region of the atrioventricular node. Note its straight course in an upward direction, and its right angle terminal branching. Just above the coronary sinus is the arteria anastomotica auricularis magna, coursing in the base of the region of the interatrial septum; it arose from the left circumflex artery near the bifurcation of the main left coronary artery.

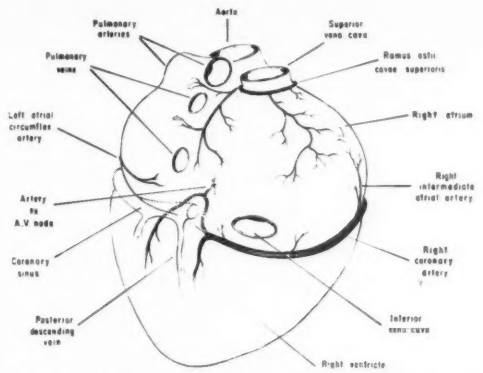


FIG. 8. Schematic illustration of the U turn of the right coronary artery beneath the coronary sinus deep to the posterior descending vein. The artery to the atrioventricular node with its terminal angle branches is shown.

these chambers. These were presumably thebesian channels, and were much more frequent in the right atrium than the left, and more numerous on the right side of the interatrial septum.

The thebesian channels in the anterior and lateral portions of the right atrium were often so numerous as to coalesce and to cast as trabeculae of plastic. The small atrial arteries in these regions often course beneath these trabeculations, temporarily disappearing from view in their course (fig. 10).

The venous channels in the interatrial septum located at the base of the superior vena cava were especially striking in that they assumed considerable size and frequently were associated with the arterial circle of the ramus ostii cavae superioris (fig. 11).

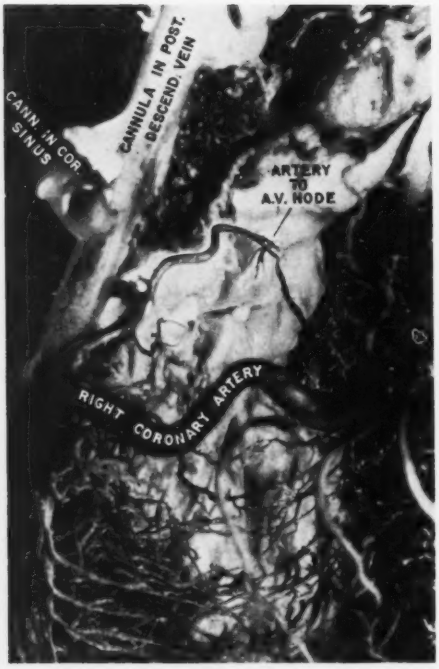


FIG. 9. The right coronary artery making its unique U turn deep to the posterior descending vein.

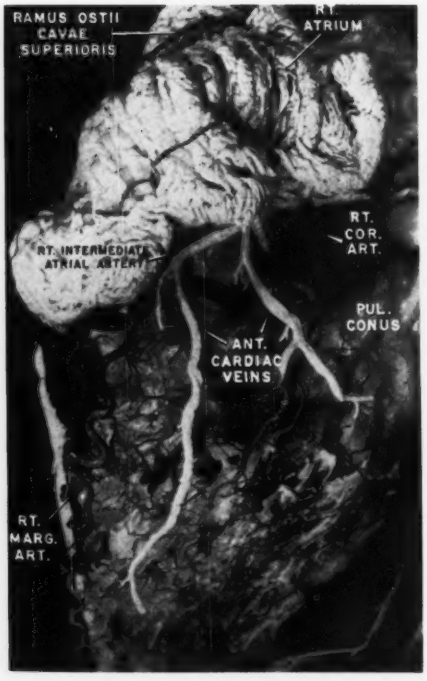


FIG. 10. The right intermediate atrial branch, showing how it is covered over in part of its course by plastic which casts the thebesian channels of the right atrium. The terminal branches of this atrial artery communicate with the arterial circle at the base of the superior vena cava.

DISCUSSION

The nature of the blood supply to the human sinoatrial node indicates in part why the clinical expressions of sinoatrial nodal ischemia are so variable. For example, whether or not sinoatrial node block develops depends, at least, upon the following 4 factors: (1) The coronary artery from which the ramus ostii cavae superioris originates, (2) whether or not an occlusion is distal or proximal to the origin of the ramus ostii cavae superioris, (3) the effectiveness of the collateral circulation to the sinoatrial node, including thebesian channels, and (4) the circulatory demands of the sinoatrial node area at the time.

Since the artery to the sinoatrial node arises much more frequently from the right coronary artery, shifting pacemaker, atrial fibrillation, sinoatrial node block and other manifestations of sinoatrial nodal ischemia should be anticipated more frequently with right coronary disease, all other factors being equal.

Incomplete atrioventricular block, Wenckebach phenomenon, and other disturbances due to malfunction of the atrioventricular node or upper bundle of His may be expressions of disease of the atrial arteries with resultant impairment of their circulation. Disturbances in function of the atrioventricular node and bundle of His are to be expected much less frequently with occlusion of the left coronary artery, since it supplied the atrioventricular node in only 10 per cent of hearts studied. The effectiveness of the collateral circulation would of course influence the degree of ischemia suffered.

Isolated lesions of the artery to either of the 2 atrial nodes have received extremely little attention from pathologists; in fact, this is true of the atrial myocardium. Segments of ventricular myocardium are routinely removed at the autopsy table for histologic examination, whereas it is unusual to study segments of atrial tissue. Nevertheless, disease

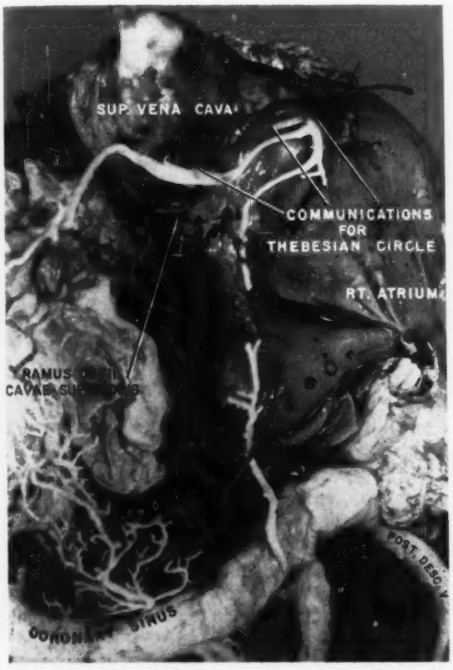


FIG. 11. The thebesian venous circle that often accompanies the arterial circle at the base of the superior vena cava. This venous circle was filled by plastic injected into the right atrium, the points of communication with the atrial lumen being indicated.

of the atrial vessels and myocardium undoubtedly occurs. Unfortunately, the incidence of such disease remains unknown. This is particularly true of atherosclerotic changes in the atrial arteries. A careful pathologic study of these vessels with such long, narrow, and tenuous courses may be as lucrative in disease processes as were surgically removed segments of the atrial myocardium and its appendage for lesions of rheumatic fever. Spontaneous atrial fibrillation in elderly patients may be a relatively infrequent expression of much more commonly present atherosclerotic disease of the ramus ostii cavae superioris.

Recent surgical interest in atrial septal defects has increased the practical importance of knowledge of the structures in and adjacent to the interatrial septum. This is particularly true of the sinoatrial node and atrioventricular node. With a detailed knowledge of the arterial supply of these nodes, proper precautions may be exercised to preserve these arteries whenever possible, and adequate consideration made when they must be ligated or otherwise occluded.

Incisions, clamping, or ligation that transgresses the anterior interatrial septal groove can only on rare occasion avoid disturbing the main circulation to the sinoatrial node. Similarly, the posterior half of the base of the interatrial septum contains the artery that nourishes the atrioventricular node; therefore, procedures involving this region may produce disturbances in atrioventricular conduction.

The peculiar U turn into the base of the posterior interatrial septum by the main right coronary artery exposes this large vessel to surgical procedures involving the interatrial septum. Traumatic occlusion of this artery would not only induce ischemia of the atrioventricular node but could also produce infarction of the entire posterior wall of the left ventricle.

It is obvious, therefore, that a detailed knowledge of the atrial circulation and its anatomy are of considerable importance, not only from the surgical point of view, but also for a better physiologic understanding of the atria and their function.

SUMMARY

The atrial coronary arteries were studied in 43 fresh normal human hearts. The largest atrial artery in man was that supplying the region of the sinoatrial node. It arose from the left coronary artery in 39 per cent and the right coronary artery in 61 per cent of the hearts. Its general course from either artery was to the anterior interatrial septum and thence to an encircling termination at the base of the superior vena cava.

A specific artery supplied the region of the atrioventricular node. It arose from the right coronary artery at the posterior junction of the interatrial and interventricular septa in 83 per cent of these hearts. The parent artery at this location made an interesting U turn beneath the posterior descending vein. This turn may be of considerable embryologic significance.

Many other atrial coronary arteries were noted but were small and variable. One of

their principal functions may be that of potential sources of collateral circulation.

The clinical significance of a knowledge of the atrial circulation is evident and was discussed.

ACKNOWLEDGMENT

We are grateful to Drs. William Eckert, Wallace Clark, and Nicholas Chetta for their cooperation in this study. Vinylite resin was generously provided by the Bakelite Division of Union Carbide Corporation, South Charleston, W. V.

SUMMARIO IN INTERLINGUA

Le arterias coronari atrial esseva studiate in 43 normal cordes human in stato frese. Le plus grande arteria atrial esseva illo que alimenta le region del nodo sino-atrial. Illo partiva ad le sinistre arteria coronari in 39 pro cento del cordes e ab le dextere arteria coronari in 61 pro cento. Su curso general, in le un e le altere caso, duceva ab le arteria de su origine verso le parte anterior del septo interatrial e postea verso un termination incirculante al base del vena cave superior.

Un arteria specific alimentava le region del nodo atrio-ventricular. Illo partiva ab le dextere arteria coronari al junction posterior del septos interatrial e interventricular in 83 pro cento del casos. In iste sito le arteria matre describeva un interessante curva in forma de U infra le descendente vena posterior. Il es possibile que iste curva possede un considerabile signification embryologic.

Numerose altere arterias coronari atrial esseva notate, sed illos esseva parve e variabile. Un de lor principal functiones es possibilemente lor capacitate potential de establir un circulation collateral.

Le signification clinic del studio del circulation atrial es evidente. Su principal aspectos es discutite.

REFERENCES

1. GRAY, H.: Anatomy of the Human Body. Ed. 25, edited by Charles M. Goss. Philadelphia, Lea & Febiger, 1948.
2. MEEK, W. J., KEENAN, M. AND THEISEN, H. J.: The auricular blood supply in the dog: I. General auricular supply with special reference to the sino-auricular node. Am. Heart J. **4**: 591, 1929.
3. KEITH, A. AND FLACK, M.: The form and nature of the muscular contractions between the primary divisions of the vertebrate heart. J. Anat. & Physiol. **41**: 172, 1907.
4. SPALTEHOLZ, W.: Die Arterien der Herzwand. Leipzig, Hirzel, 1924.
5. CRAINICIANU, A.: Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgangigkeit. Virchows Arch. **238**: 1, 1922.
6. GROSS, L.: The Blood Supply to the Heart. New York, Paul B. Hoeber, 1921.
7. MOORE, R. A.: The coronary arteries of the dog. Am. Heart J. **5**: 743, 1930.
8. PIANETTO, M. D.: The coronary arteries of the dog. Am. Heart J. **18**: 403, 1939.
9. KAZZAZ, D. AND SHANKLIN, W. M.: The coronary vessels of the dog demonstrated by colored plastic (vinyl acetate) injections and corrosion. Anat. Rec. **107**: 43, 1950.
10. HALPERN, M. H.: The arterial supply to the nodal tissue in the dog heart. Circulation **9**: 547, 1954.
11. SCHLESINGER, M. J.: An injection plus dissection study of coronary artery occlusions and anastomoses. Am. Heart J. **15**: 528, 1938.
12. ZOLL, P. M., WESSLER, S. AND SCHLESINGER, M. J.: Interarterial coronary anastomoses in the human heart, with particular reference to anemia and relative cardiac anoxia. Circulation **4**: 797, 1951.
13. WHITTEN, M. B.: A review of the technical methods of demonstrating the circulation of the heart. Arch. Int. Med. **42**: 846, 1928.
14. MCCLENAHAN, J. L. AND VOGEL, F. S.: The use of fusible metal as a radiopaque contrast medium and in the preparation of anatomical castings. Am. J. Roentgenol. **68**: 406, 1952.
15. WAGNER, A. AND POINDEXTER, C. A.: Demonstration of coronary arteries with nylon. Am. Heart J. **37**: 258, 1949.
16. SMITH, J. R. AND HENRY, M. J.: Neoprene latex demonstration of the coronary arteries. J. Lab. & Clin. Med. **30**: 462, 1945.
17. STERN, H., RANZENHOFER, E. R. AND LIEBOW, A. A.: Preparation of vinylite casts of the coronary vessels and cardiac chambers. Lab. Investigation **3**: 337, 1954.
18. BAROLDI, G., MANTERO, O. AND SCOMAZZONI, G.: The collaterals of the coronary arteries in normal and pathologic hearts. Circulation Research **4**: 223, 1956.
19. KOCH, W.: Ueber die Blutversorgung des Sinusknotens und etwaige Beziehungen des letzeren zum Atrioventrikularknoten. München. med. Wchnschr. **56**: 2362, 1909.
20. KUGEL, M. A.: Anatomical studies on the coronary arteries and their branches. I. Arteries anastomotica auricularis magna. Am. Heart J. **3**: 260, 1927.
21. WALLS, E. W.: Dissection of the atrioventricular node and bundle in the human heart. J. Anat. **79**: 45, 1945.

SPECIAL ARTICLE

Influence of Some Factors on Development of Experimental Cholesterol Atherosclerosis

By A. L. Myasnikov

THIS paper is a brief outline of the results of research conducted for many years by my associates at the Institute of Therapy of the Academy of Medical Sciences in Moscow. The purpose of these studies was to observe the influence of different factors on the development of experimental atherosclerosis produced by feeding rabbits with cholesterol according to N. N. Anichkov's method. We have studied factors that both increased and retarded the development of experimental cholesterol atherosclerosis.

Our general program may be represented in the following way. Each study of the effect of a certain agent administered in combination with cholesterol comprised 2 groups of animals: control and experimental. Both control and experimental groups of rabbits received *per os* an equal amount of cholesterol together with food. The amount ranged from 0.1 to 0.2 Gm. per Kg. of weight daily for 100 days. In addition, the experimental groups received some other factor during the whole period or part of it. Furthermore, additional control studies were made of the possible effect on the vessels of the factor alone without administration of cholesterol. In every series of experiments the animals were of approximately similar weight, age, and sex.

The following factors have been studied: (1) some vitamins; (2) neurotropic drugs acting on the higher parts of the nervous system; (3) anticoagulants; and (4) anoxia and muscular exercise.

The blood cholesterol was systematically determined in all animals at intervals from 10 to 15 days.

At the end of the experimental period the rabbits were killed, and the aorta and the coronary arteries were examined. The arteries were immersed for a certain time in a solution of Sudan III so that the lipoid-infiltrated parts of the blood vessels were colored bright red. The degree of lipoidosis was graded on a scale of 1 to 4 plus.

Histologic examination was made in some cases.

Effect of Vitamins

Among the various vitamins, some, such as vitamin B_1 and riboflavin, exercised no definite influence on the degree of development of experimental atherosclerosis. Other vitamins, such as vitamin A and nicotinic acid, influenced the development of experimental atherosclerosis when administered in doses larger than the usual clinical doses. On the other hand, 2 vitamins, vitamin D_2 and vitamin C (ascorbic acid), had a very marked effect.

Vitamin D_2. The investigations conducted by M. V. Bavina showed that the administration of vitamin D_2 with food drastically increased both the degree and rate of development of alimentary hypercholesterolemia and the intensity of the aortic lipoidosis. These investigations were made on 32 rabbits. The animals received daily 10,000 units of vitamin D_2 (0.25 mg. of crystalline vitamin D_2).

Whereas the cholesterol content in the control group that received cholesterol only rose at the end of the experiment 88 to 300 per cent and averaged 183 per cent, the concentration of cholesterol in the experimental group (vitamin D_2 + cholesterol) rose 272 to 1,821 per cent and averaged 689 per cent (fig. 1). The cholesterol content in the group of animals that

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This paper has been submitted at the suggestion of Dr. Irving S. Wright, who became acquainted with the work of Professor Myasnikov during a visit to Moscow in October 1956.

received only vitamin D_2 without cholesterol hardly changed at all at the end of the standard time period.

In the control group of animals that received only cholesterol, the intensity of the aortic lipoidosis was generally 2 plus and, less frequently, 1 or 3 plus; in the experimental group of rabbits (cholesterol + vitamin D_2) the lipoidosis was far more intensive and was appraised 4 plus and less frequently 3 plus (fig. 2). No lipoid deposits were observed macroscopically in the aorta of animals that received vitamin D_2 in the same doses but no cholesterol.

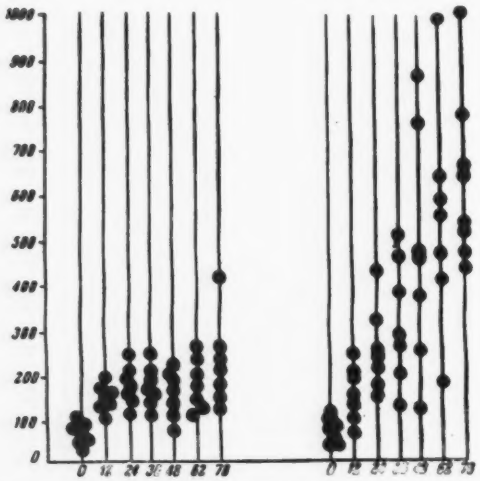

FIG. 1. The influence of vitamin D_2 on the blood cholesterol level in cholesterol-fed rabbits. *Ordinate* represents cholesterol in mg. per cent; *abscissa*, days. cholesterol only (*left*), cholesterol plus vitamin D_2 (*right*).

We do not deal here with the problem of the influence of vitamin D_2 on the development of necrosis and calcinosis of the muscular membrane of the blood vessels. In our series of experiments, with the doses of vitamin D_2 used, such changes were observed only occasionally, were slight, and were not related in any way to lipoid infiltrates.

The mechanism whereby vitamin D_2 stimulates the development of vascular lipoidosis has not as yet been sufficiently studied.

Ascorbic Acid. According to the investigations conducted by I. A. Myasnikova, which I reported as far back as 1947 at the Thirteenth Congress of Soviet Therapeutists, and which were subsequently confirmed by a number of clinical institutions, ascorbic acid influences very markedly the development of experimental atherosclerosis of the aorta in rabbits as well as alimentary cholesterolemia, but in a direction opposite to that of vitamin D_2.

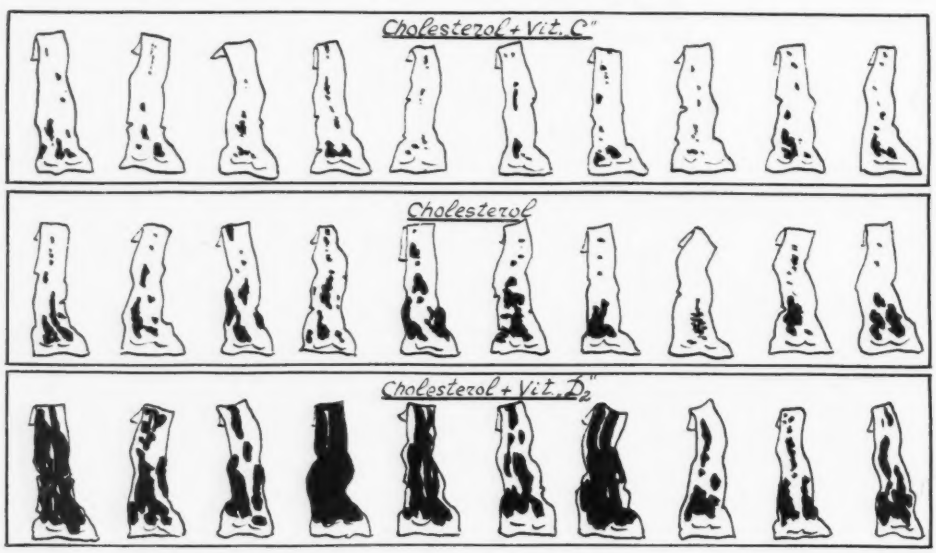

FIG. 2. The effects of cholesterol, vitamin C, and vitamin D on atherosclerosis of the aorta in rabbits.

Ascorbic acid reduces the development of hypercholesterolemia and lessens and retards the development of experimental lipoidosis of the aorta in rabbits.

These experiments were performed on 35 rabbits. Ascorbic acid was administered *per os* in doses from 0.1 to 0.2 Gm. At the end of the experiment, the level of cholesterol in this series of experiments in the control group that received only cholesterol rose 2 to 4 times and averaged 238 per cent. In the experimental group receiving cholesterol plus ascorbic acid the hypercholesterolemia increased more slowly and reached its maximum later. In some experiments cholesterolemia changed comparatively little during the first 2 months and generally doubled or trebled only toward the end of the experiment. The average increase in this group amounted only to 116 per cent (fig. 3).

At autopsy these rabbits revealed differences in the lipoidosis in the aortas similar to the differences observed in the hypercholesterolemia. Whereas the intensity of lipoidosis of the aorta in the control group could be defined by 2 plus and but rarely by 3 plus, the intensity of lipoidosis in the experimental group could be appraised but by 1 and rarely by 2 plus, while in a number of experiments no lipoid deposits were observed macroscopically in the aorta (fig. 2).

The following reservation should be made in this connection. It is well known that rarely lipoidosis may not develop in blood vessels even when cholesterol alone is administered in large doses. Evidently such rabbits are resistant to the development of atherosclerosis. This fact is one of the proofs of the great importance of some internal endogenous mechanisms that participate in the regulation of cholesterol metabolism in the organism and change the nature and degree of the assimilation of food cholesterol.

Absence of marked lipoidosis was encountered far more frequently when ascorbic acid was administered in combination with cholesterol. The mechanism whereby ascorbic acid retards the development of atherosclerosis has been specially studied by us. According to the findings of T. Y. Sidelnikova, the administration of ascorbic acid augments the amount of

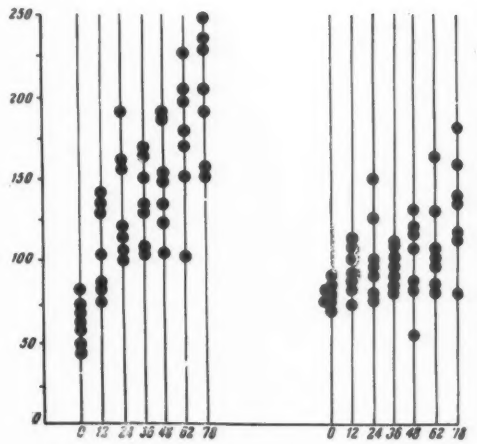

FIG. 3. The influence of ascorbic acid on the blood cholesterol level in cholesterol-fed rabbits. *Ordinate:* Cholesterol in mg. per cent. *Abscissa:* Days. Cholesterol only (*left*); cholesterol plus ascorbic acid (*right*).

ketonic bodies in blood and stimulates the metabolism of fats and lipoids. There is reason to believe that, by intensifying the functional capacity of the liver, ascorbic acid stimulates the secretion of cholesterol with the bile. According to the observations by L. A. Typina, the intravenous administration of ascorbic acid to patients with atherosclerosis and hypertonic disease and a high content of cholesterol in the blood leads to a markedly lowered cholesterolemia. Simultaneously a greater concentration of cholesterol in the duodenal contents and the excrements is recorded (fig. 4).

It may be assumed that ascorbic acid reduces hypercholesterolemia and weakens the development of lipoidosis of the blood vessels both by influencing the oxidizing and restorative processes and by intensifying the excretion of cholesterol from the body.

Effect of Neurotropic Drugs

A study of the influence of pharmacologic agents changing the functions of the higher parts of the nervous system on the development of experimental atherosclerosis and on cholesterol metabolism was of particular interest for many reasons. First of all, the importance of the nervous factor in the pathogenesis

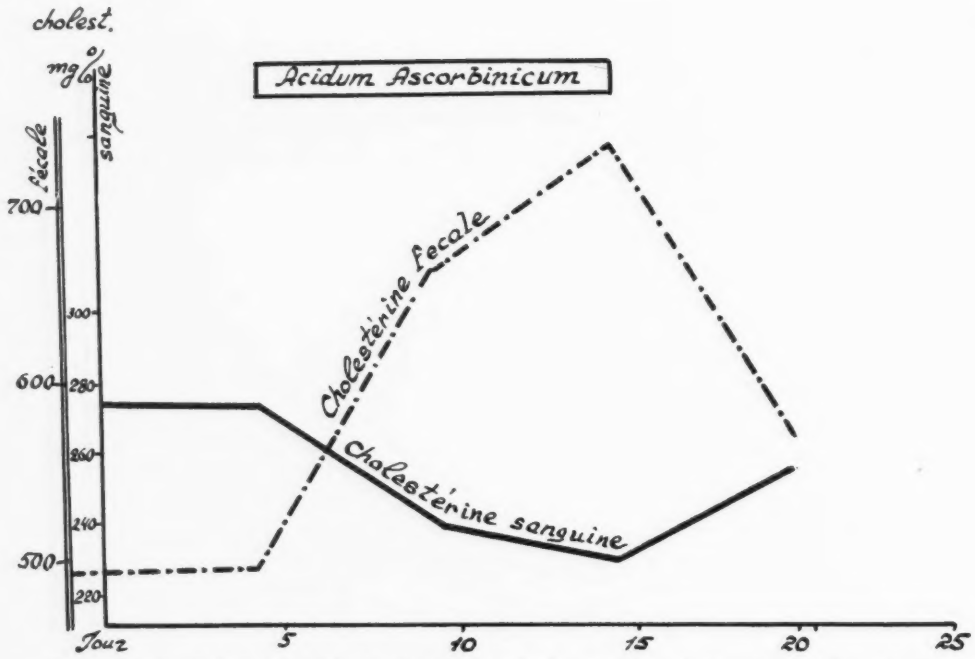

FIG. 4. The level of cholesterol in the blood and in the feces before and after the administration of ascorbic acid.

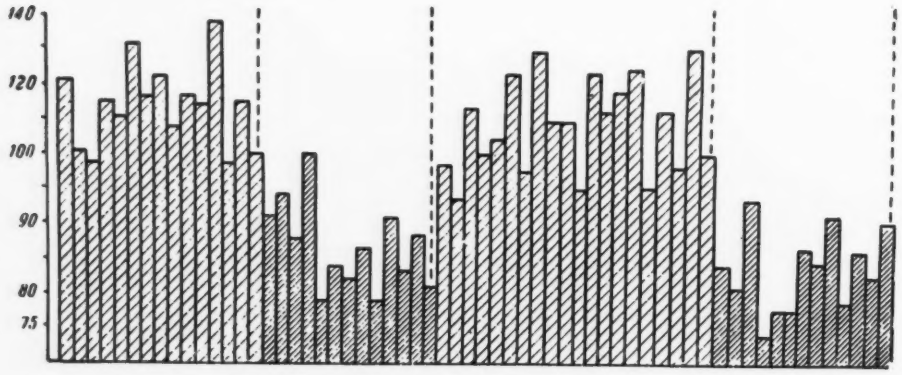

FIG. 5. Fluctuations of arterial blood pressure, mm. Hg, (*ordinate*) in rabbits with experimental atherosclerosis treated with barbiturates. Columns 2 and 4 show drop in pressure after phenobarbital.

of atherosclerosis has as yet been very little investigated. Secondly, it has long been assumed in clinical practice that there undoubtedly exists a connection between disturbances in the central nervous system and the appearance of atherosclerosis. Thirdly, insufficient attention has been given to the role of endogenous factors in the development of experimental atherosclerosis. The administration of drugs acting on the nervous system during the production of atherosclerosis is of interest as an effort to influence the endogenous regulating mechanisms.

Pharmacologic agents were utilized that in-

ensify the processes of excitation; others were used that weaken them or intensify inhibitory processes. It was interesting to compare the influence of these neurotropic drugs on the development of experimental atherosclerosis. These investigations were conducted by a number of researchers (Y. T. Pushkar, T. D. Tsybikmakher, I. K. Shkhvatsabaya, and L. A. Myasnikov).

One of the series of experiments was devoted to the study of 2 neurotropic substances acting in opposite directions: phenobarbital (Luminal) and phenamine (Benzedrine). Phenobarbital in doses of 0.2 Gm. and phenamine in doses of 0.04 Gm. were administered periodically throughout the experimental period.

The blood cholesterol and lecithin and the blood pressure were measured at definite intervals throughout the period of the experiment. For blood pressure measurements the carotid artery was brought out into a skin strip.

Phenobarbital little changed the cholesterol and lecithin content in the blood, tending rather to reduce the concentration of either lipoid. Under the influence of phenobarbital the behavior of the rabbits changed; they lost some of their agility and remained most of the time in a semi-drowsy state. As phenobarbital was administered, the arterial systolic and diastolic pressures regularly dropped 20 to 40 mm. Hg (fig. 5). The fluctuations of blood pressure, which were quite marked in the rabbits of the control group, considerably diminished in this case.

The development of atherosclerotic changes in the aorta in the rabbits receiving phenobarbital was quite markedly reduced: only 1 of 10 rabbits in the group showed 3 plus; in 7 the atheromata were manifest to a medium degree (2 plus), and in 2 to a slight degree (1 plus) (fig. 6).

The administration of phenamine (Benzedrine) led to an abrupt rise in the excitability of the central nervous system, to greatly increased instability of arterial pressure, and, in a number of experiments, to rises in arterial pressure.

The cholesterolemia increased considerably. Whereas in the control group of animals (only cholesterol) the maximum cholesterol content

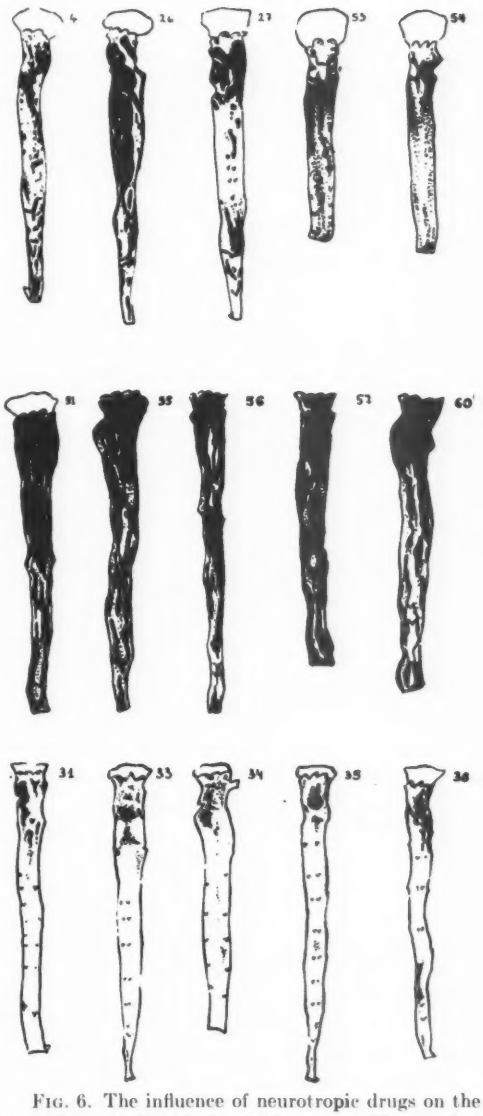

FIG. 6. The influence of neurotropic drugs on the experimental lipoidosis of the aorta. First series, control (only cholesterol); second series, cholesterol plus phenamine; third series, cholesterol plus phenobarbital.

in the blood was 800 mg. per cent at the end of the experimental period, the maximum concentration of cholesterol in the blood of most rabbits that received phenamine increased to 2,100 mg. per cent (fig. 7). Accordingly, a more extensive development of aortic lipoidosis was re-

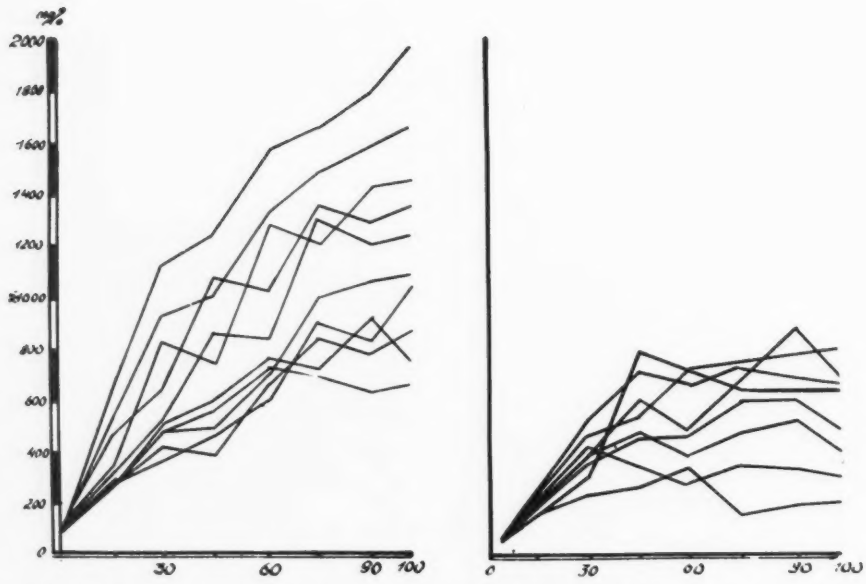

FIG. 7. Influence of neurotropic drugs on the blood cholesterol level (*ordinate*) in experimental atherosclerosis. *Left*, cholesterol plus phenamine; *right*, cholesterol only.

corded in the experimental group (cholesterol plus phenamine) than in the controls (fig. 6). Of the 10 rabbits that received cholesterol with phenamine, lipoidosis in 6 of them was appraised as 4 plus and in 4 as 3 plus.

The administration of phenamine led to a more pronounced degree of lipoid infiltration at some points and also to a more diffuse lipoidosis of the aorta.

A series of experiments was performed in which, besides cholesterol, not only phenobarbital and phenamine were applied, but simultaneously choline as well. It is known that choline reduces to some extent the development of experimental cholesterol atherosclerosis in rabbits. It was ascertained from this series of experiments on 20 animals that this effect becomes more marked when choline is combined with phenobarbital, and, quite the contrary, it is blocked when phenamine is administered simultaneously. In these experiments the influence of the neurotropic factors and choline on atherosclerosis was studied not only in the aorta, but also in the large coronary arteries, which exhibited the same changes as the aorta, though to a lesser degree.

The next series of investigations was devoted to studying 3 other drugs: amobarbital (Amytal) sodium, caffeine, and chloral hydrate.

When cholesterol was administered with food, the level of cholesterol in the blood of the control group reached 450 to 550 mg. per cent at the end of the experimental period, and in some cases 800 to 900 mg. per cent. In most instances atherosclerosis was quite pronounced. In the experimental group receiving cholesterol and caffeine the level of cholesterol in the blood differed but little from that in the control group. Atherosclerotic changes in the former group likewise approximated those in the control group.

Cholesterolemia of a slighter degree was recorded in the experimental group when amobarbital sodium was administered in addition to cholesterol. In some experiments no increase was observed (fig. 8). Similar results were obtained in the group receiving chloral hydrate in addition to cholesterol. The level of cholesterol in the blood rose rather slightly, despite systematic administration of cholesterol with food. In all the rabbits the aorta lipoidosis

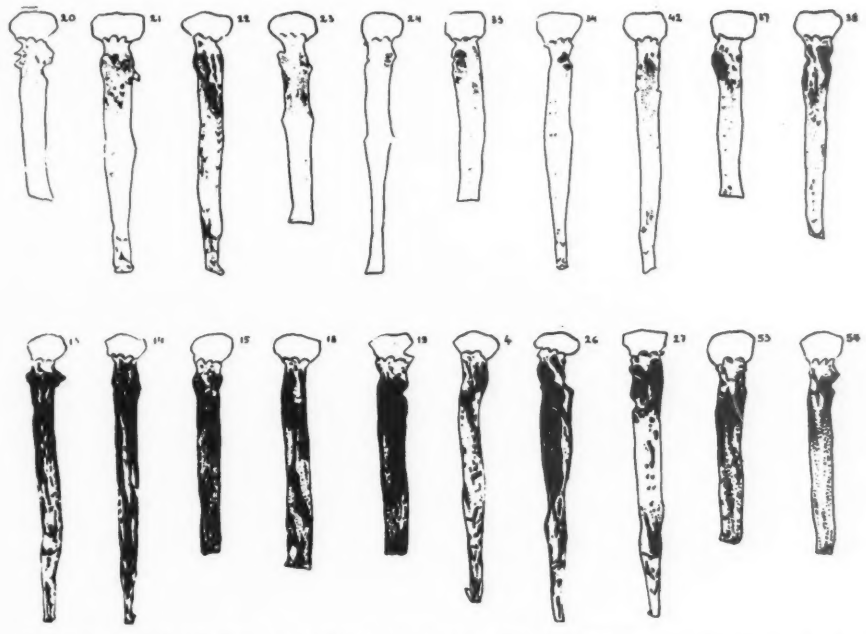

FIG. 8. Aortas of cholesterol-fed rabbits treated with amobarbital sodium (*top series*); cholesterol only (*bottom series*)

proved to be slight; in 2 cases no lipoidosis was recorded at all.

Blood pressure was systematically measured in these groups of rabbits. The caffeine rabbits exhibited greater fluctuations of blood pressure than the controls. The Amobarbital sodium and chloral hydrate groups of rabbits showed a pronounced lowering of blood pressure and reduced fluctuations.

Under the influence of soporifics, the behavior of the rabbits changed: they became less agile, indifferent to the surroundings, and inert. In the amobarbital sodium series after the administration of the drug sleep set in daily, and lasted from 2 to 5 hours.

These findings lead us to the conclusion that when the excitability of the central nervous system is reduced, respiratory inhibition is intensified, an abrupt decrease of alimentary hypercholesterolemia is observed, and of particular importance, a decreased lipoidosis of the blood vessels occurs. It is difficult to state whether this reduction is related to lowered alimentary hypercholesterolemia or to the reduced level of blood pressure and to a decrease in its fluctuations or to both.

Apart from the above experimental investigations, clinical observations also were made on the influence of neurotropic drugs on serum cholesterol level of patients with hypertonic disease and atherosclerosis. Patients with a pronounced rise in the blood cholesterol were observed. Various drugs were administered, some calming the nervous system by reducing the excitability of the higher parts of the nervous system or increasing inhibition, such as phenobarbital, chloral hydrate, and amobarbital sodium, and others exciting the nervous system, such as phenamine and caffeine. The drugs were administered in comparatively large doses: Phenobarbital, 0.3 to 0.2 Gm.; chloral hydrate, 1 Gm.; Amobarbital sodium, 0.3 Gm.; caffeine, 0.3 Gm.; and phenamine, 20 mg. Observations were made in 128 patients. In some individuals different drugs were employed, thus facilitating the comparison of their effect.

The observations were of 2 kinds: short ex-

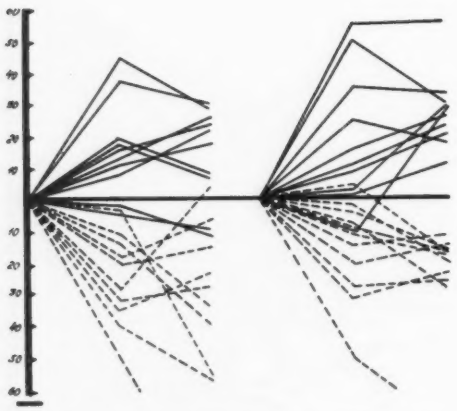

FIG. 9. Influence of neurotropic drugs on the blood cholesterol of patients with hypertension and atherosclerosis: caffeine (*left upper*); phenamine (*right upper*); amobarbital sodium (*left lower*); chloral hydrate (*right lower*). Changes in blood cholesterol levels are expressed in percentages of initial level (*ordinate*).

periments with blood cholesterol levels measured 1, 2, or 3 hours after single doses and prolonged observations of the blood cholesterol levels for a week or 2, when, after daily doses, the results of these observations proved to be similar to those of experimental observations. The drugs reducing the excitability of the central nervous system and inhibiting its function (amobarbital sodium, chloral hydrate, and phenobarbital), reduced the blood cholesterol level; the drugs exciting the activity of the central nervous system (phenamine and caffeine), exerted an influence in the opposite direction, raising the cholesterolemia (fig. 9). These changes were revealed most clearly after single doses; when administration was prolonged, changes in cholesterolemia appeared less pronounced, though in the same direction.

Our findings confirm the conclusion that the cholesterol content in the blood is controlled by the central nervous system. The opposite nature of the effects on the central nervous system of the neurotropic pharmacologic drugs caused opposite effects on the cholesterolemia and experimental lipoidosis of the vessels. It is difficult to believe that the consistent pharmacologic effects could be unrelated to their central influence, but due to some other collateral influence on the internal organs, i.e., the liver and the endocrine glands, although such influences can hardly be left out of account altogether.

EFFECT OF ANTICOAGULANTS

It is common knowledge that anticoagulants play a significant role in treating of patients with myocardial infarction, one of the most important manifestations of atherosclerosis. Attention has been centered on the effect of anticoagulants in retarding or preventing thromboembolic phenomena. However, the problem has recently been raised as to the possible influence of anticoagulants on the development of the atherosclerotic process itself. In a series of experiments we administered daily 30 to 60 mg. of heparin intravenously in prolonged courses of treatment, in addition to the regular doses of cholesterol introduced with food. In other experiments, another anticoagulant, neodicoumarin (Pelentan) was administered instead of heparin in doses of 20 to 40 mg. per Kg. of weight, simultaneously with the cholesterol.

Control experiments were carried out with the administration of cholesterol only; the results obtained were quite similar to those produced in the other control series, both in respect to the degree of alimentary hypercholesterolemia and the pronounced lipoidosis of the aorta and other arteries.

Finally, control experiments were conducted with the administration of heparin or neodicoumarin alone, without simultaneously administered cholesterol. No markedly pronounced lipoid deposits were discovered in the aorta walls in this group.

The findings of the investigations are shown in diagrams. Figure 10, for example, demonstrates the fluctuations of the blood cholesterol content in various groups of rabbits. No sharp difference was apparent between the development of alimentary cholesterolemia in the control series (cholesterol only) and the series where neodicoumarin was administered in addition to cholesterol. In the cholesterol plus heparin group of experiments, a somewhat less pronounced alimentary hypercholesterolemia was observed.

The degree of atherosclerosis in the group of

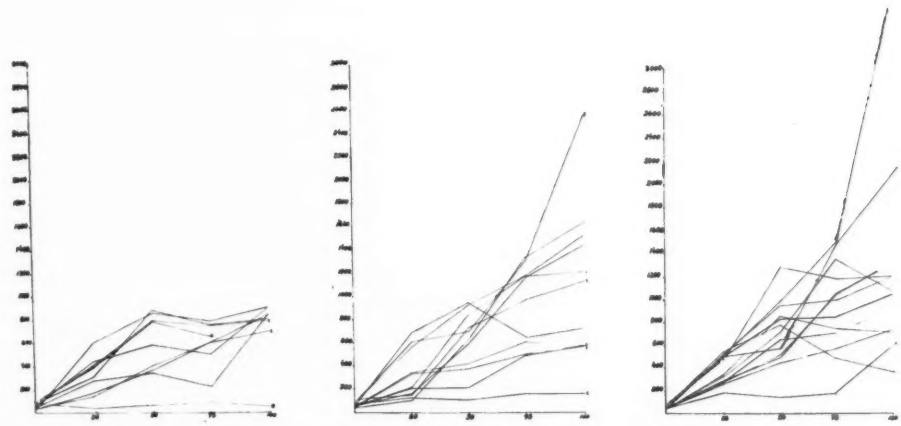

FIG. 10. Blood cholesterol in rabbits treated with cholesterol plus heparin (*left*); cholesterol only (*center*). Cholesterol plus Dicumarol (*right*). Blood cholesterol mg. per cent (*ordinate*); days of feeding (*abscissa*).

experiments with neodicoumarin plus cholesterol was quite similar to the experiments in the control group (i.e., cholesterol only), but sometimes the degree of lipoidosis was more pronounced.

Different results were obtained when heparin was administered in addition to cholesterol. In the "heparin" group the degree of lipoidosis of the aorta and other arteries was reduced compared with the group where cholesterol only was administered, or in the group of cholesterol plus dicoumarin, as shown in figure 11 (borrowed from the material collected by A. P. Efimova, who conducted this part of the investigations).

Hence the data testify that heparin possesses the valuable supplementary property of reducing the development of experimental cholesterol atherosclerosis. Dicoumarin, the other widely used anticoagulant, is devoid of this property.

The influence of heparin on the development of experimental atherosclerosis was of approximately the same degree when smaller (30 mg.) and larger (60 mg.) doses were used. We have not as yet sufficient material at our disposal to discuss the mechanism by which heparin achieves this effect. It is noteworthy that in the heparin series, the blood concentration of cholesterol was slightly less than in the control series. Consequently, heparin reduces the development of experimental lipoidosis not only through reducing the degree of alimentary hypercholesterolemia, but by means of some other mechanisms as well.

Additional measurements in similar experiments of the phospholipid content have not given any clue to the solution of the problem. The administration of heparin produces substantial changes in the lipoprotein fractions. The injection of heparin causes a marked reduction of the β-lipoprotein fraction both in the experiments on the rabbits and in patients with hypercholesterolemia. The evaluation was made by means of paper electrophoresis. The reduction persists for several hours after the injection and can also be recorded after repeated injections.

The administration of other anticoagulants, preparations of the decoumarin group, does not lead to such a drop in the content of both cholesterol in the blood and β-lipoprotein in patients suffering from atherosclerosis and hypertonic disease.

Effect of Anoxia and Physical Exercise

This series of experiments was performed not only to ascertain the influence of these factors on the development of the atherosclerosis, but also to study the dystrophic and sclerotic changes in the myocardium. This research was carried out by N. N. Kipshidze, Assistant Professor of the Institute of Therapy.

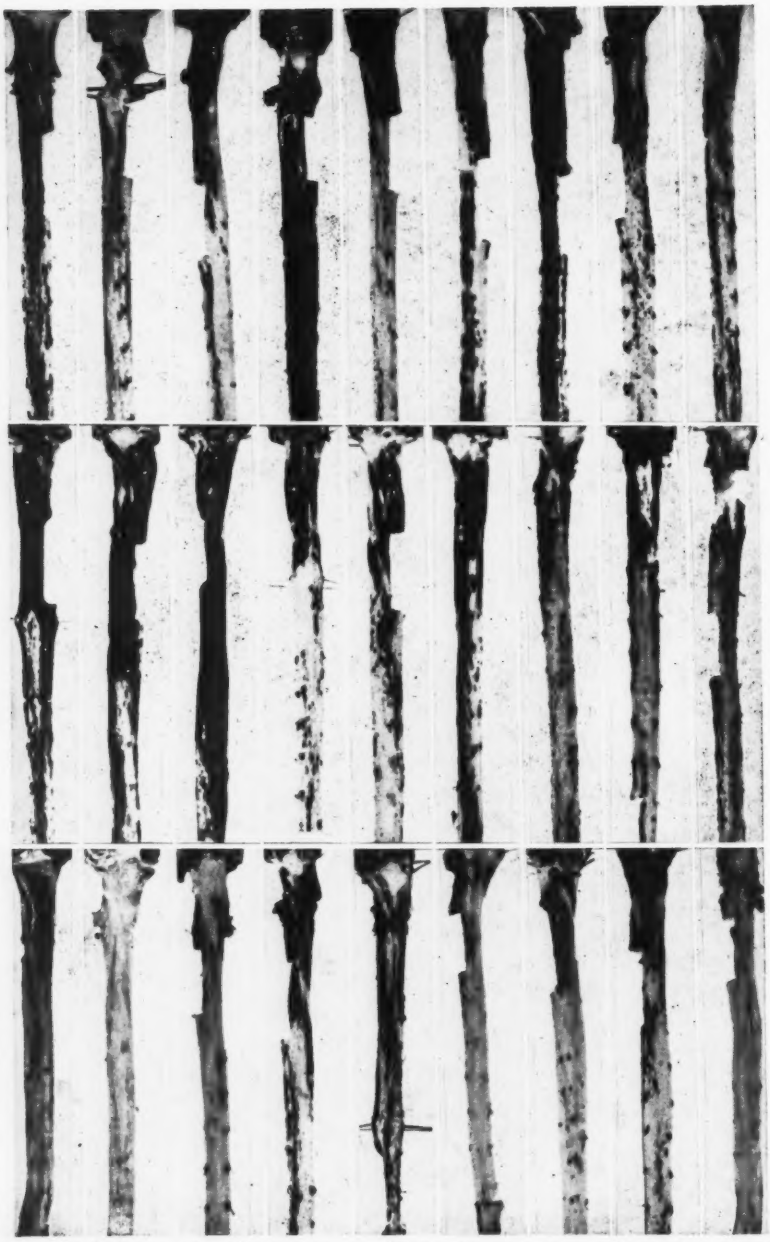

FIG. 11. The influence of anticoagulants on the development of experimental atherosclerosis. *Top series*, cholesterol; *middle series*, cholesterol plus Dicumarol; *bottom series*, cholesterol plus heparin.

Experiments with hypoxia were performed on 27 rabbits that were divided into 3 groups. The first group, consisting of 10 rabbits, received cholesterol daily as long as 6 months in comparison with the preceding series of experiments. The second group, comprising 12 rabbits, received cholesterol daily during the same period, and during the last 4 months was kept for 3 to 6 hours daily in chambers with a reduced amount of oxygen (up to 12 per cent). The third group, consisting of 5 rabbits, did not receive any cholesterol; during 4 months they were kept daily for 3 to 4 hours in chambers with a reduced amount of oxygen. The cholesterol level of the blood was analyzed in each rabbit twice a month. At the end of 6 months the rabbits were killed, and their aortas, coronary arteries, and myocardium were studied morphologically.

Under the influence of oxygen starvation, the cholesterol content in the blood of the rabbits that received cholesterol rose much more than in the control group receiving the same doses of cholesterol, but not subjected to oxygen starvation. The factor of anoxia appears to have a drastic effect on the endogenous mechanisms of metabolism, which results in insufficient assimilation of cholesterol administered with food, and accumulation in the blood in greater quantities.

In conformity with the changes in blood cholesterol, oxygen starvation resulted in a pronounced lipoidosis of the aorta and the coronary arteries of the heart (figs. 12 and 13). The aortas of this group of rabbits were covered with atherosclerotic atheromas confluent one with another and prominent above the surface of the intima. In most experiments atherosclerosis of the coronary arteries was also markedly reduced in those rabbits kept in low oxygen chambers.

In the rabbits receiving cholesterol and kept in low oxygen chambers the myocardium showed disseminated necrosis that was confluent in several areas. In most cases these necroses were subendocardial and greatest in the left ventricle, notably in the papillary muscles. Atherosclerosis of the aorta and coronary arteries was much less pronounced in the rabbits that received only cholesterol—

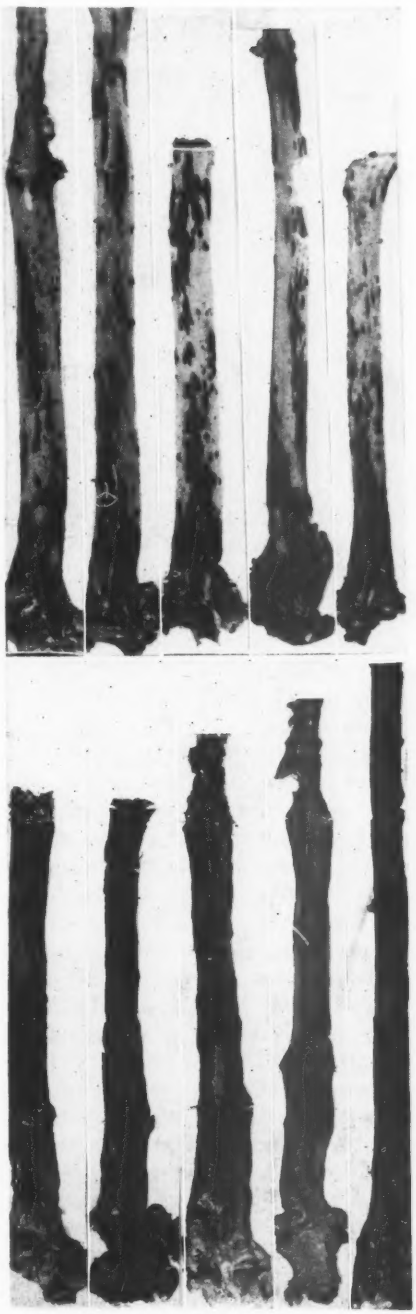

FIG. 12. Atherosclerosis of the aorta in rabbits. *Top*, in cholesterol-fed rabbits. *Bottom*, in cholesterol-fed rabbits that were kept in chambers with reduced oxygen content.

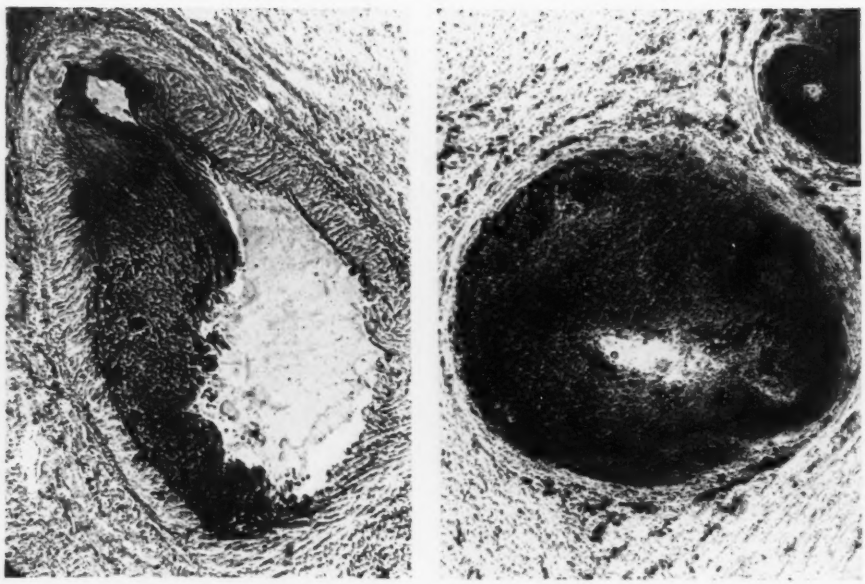

FIG. 13. Atherosclerotic plaques in the left coronary artery. *Left*, in a rabbit fed cholesterol. *Right*, in a cholesterol-fed rabbit kept in a chamber with reduced oxygen content.

only moderate focal cardiosclerosis was recorded.

The rabbits that received no cholesterol but were kept in chambers with a reduced amount of oxygen exhibited no signs of atherosclerosis of the aorta or coronary arteries; small proliferations of histiocytes occurred, however, in the myocardium.

The experiment with physical exercise was performed on 43 rabbits of the same breed. They were divided into 3 groups. The first group of 10 rabbits, the controls, received cholesterol only for 6 months; the second group, numbering 25, received daily for the same period cholesterol and physical exercise in an electric treadmill until signs of marked fatigue appeared; the third group of 8 rabbits received no cholesterol but was subjected daily to the same physical exercise for 6 months. Examination of the experimental animals was conducted in the same way as in the group of rabbits subjected to anoxia.

The rabbits subjected to physical exercise as well as cholesterol feeding showed a marked decrease of the blood cholesterol as compared with the group of rabbits that only received cholesterol. It appears that the physical exercise by intensifying metabolism in the body, results in a more intensive assimilation of alimentary cholesterol and thereby lowering of its level in the blood. Morphologic examination of the aorta and coronary arteries proved that the physical exercise reduced to some extent the development of atherosclerotic changes. These findings might serve as a proof of the beneficial effect of physical exercises and sports in preventing atherosclerosis and conform to the conclusions derived from general medical practice.

Quite substantial changes were, however, recorded in the myocardium in the series of rabbits given physical exercise in addition to the administration of cholesterol. Focal necrosis both small and extensive, as well as sclerotic changes, were observed mainly in the muscle of the left ventricle, but sometimes in the right ventricle as well. In some cases the necroses were so extensive that myocardial infarction might be supposed (fig. 14).

In some cases the myocardium exhibited quite extensive cicatricial areas apart from fresh necrotic changes (fig. 15). In one experi-

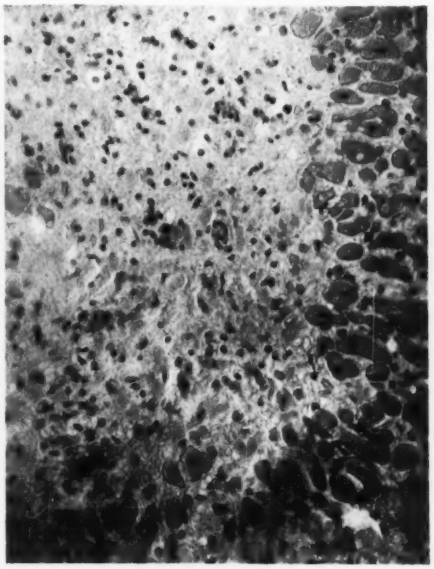

FIG. 14. Large region of necrosis in the myocardium with a mild cell infiltration in a rabbit that received cholesterol in combination with physical strain for a 6-month period.

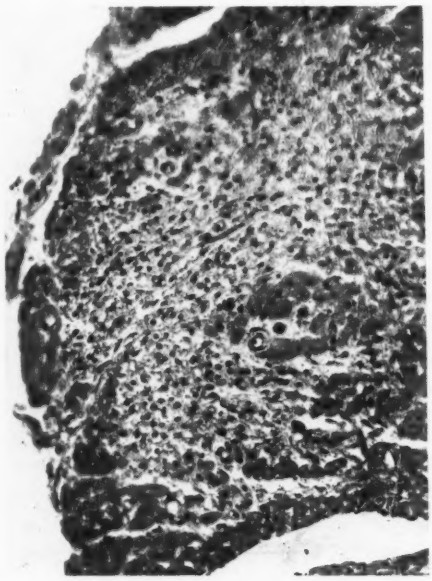

FIG. 15. Sclerotic areas after myocardial necrosis in a rabbit that received cholesterol and physical strain for a 3-month period.

FIG. 16. Aneurysm of the left ventricle in a rabbit with experimental atherosclerosis of the coronary arteries.

ment the thinning of the anterior lateral wall of the left ventricle was recorded and resulted in an aneurysm of the ventricle (fig. 16).

In all instances in which extensive necroses were found, pronounced atherosclerosis and stenosis of the coronary arteries were seen. No pathologic changes except hypertrophy of the myocardium were recorded in the rabbits given physical exercise alone without administration of cholesterol. Cardiosclerosis was slightly manifest in the rabbits receiving cholesterol only, but no physical exercise. Hence, in spite of the fact that physical exercise itself reduces the degree of alimentary cholesterolemia; in spite of the fact that lipoidosis of the aorta and coronary arteries does not attain a high degree but proves to be less pronounced than in the control group which received cholesterol only, the changes in the myocardium appear to be drastic in this series of experiments. These myocardial changes are disproportionately greater than the degree of coronary atherosclerosis. These changes appear to depend to some extent on the functional overstrain of the myocardium under conditions of physical

exercise, but are observed only with organic changes of the coronary arteries, and are in this case of an atherosclerotic nature. It may be admitted, therefore, that both the factor of atherosclerosis of the coronary arteries and that of the functional overstrain of the myocardium are equally indispensable for the development of these necrotic and cicatricial changes. Atherosclerosis itself, even when pronounced, or similar physical exercise alone in rabbits without atherosclerosis, does not produce this type of myocardial infarction.

It appears to us that these investigations set up a new model of experimental myocardial infarction, which, by the conditions of its pathogenesis, are in principle quite close to the pathologic process underlying myocardial infarction in man.

Conclusions

This research has supplied us with convincing proof that it is quite possible to change the course of development of cholesterol atherosclerosis under experimental conditions. We have become convinced that a number of chemical substances, including food (vitamins) and medicinal (neurotropic drugs and anticoagulants) drugs may either lessen or increase the development of atherosclerosis.

Apart from this, we have become convinced that such general physiologic factors as anoxemia and physical exercise may also affect the course of the atherosclerotic process in experiments. These factors are of importance for prophylaxis and therapy in that they decrease and retard the development of atherosclerosis. These effects may be considered useful to some degree in preventing atherosclerosis in man as well—we attach particular importance to ascorbic acid in this respect.

There is no doubt, however, that negatively acting factors, i.e., influences that intensify atherosclerosis, also appear to play a significant role. From the viewpoint of preventive medicine, certain measures should be avoided in order to eliminate these influences.

In addition to influencing atherosclerosis of the vessels actively, one should bear in mind that it is possible to affect the state of tissues that suffer the most during the development of atherosclerosis, notably the myocardium. Our research has shown that the cholesterol factor itself, or, to be more precise, the degree of development of atherosclerosis, does not determine to the full the deranged function and structure of the myocardium, although it is a major factor in this derangement. Of particular importance in the development of the pathology of myocardium in the presence of atherosclerosis are supplementary unfavorable factors, such as physical overstrain or anoxia.

The material presents some illustrations pointing to the possibility of influencing the development of experimental atherosclerosis in a purely nervous way, through pharmacologic effects on the higher parts of the central nervous system. If it were possible, even though approximately, to correlate these findings with clinical experience, it would then follow that excessive excitation or stimulation exerts an unfavorable effect in the sense of increasing or hastening the development of atherosclerosis, while reduced excitability of the higher components of the nervous system associated with a state of inhibition acts favorably, tending to retard or decrease the development of atherosclerosis.

Summario in Interlingua

Le hic-reportate recercas provide provas definitive pro le possibilitate de alterar sub conditiones experimental le curso del disveloppamento de atherosclerosis a cholesterol. Nos ha convincite nos que un numero de substantias chimic—incluse alimentos (i.e. vitaminas) e medicamentos (i.e. drogas neurotropic e anticoagulante)—es capace a reducer o a augmentar le disveloppamento de atherosclerosis.

In plus, nostre recercas ha convincite nos que factores physiologic general como per exemplo anoxemia e exercitios physic pote equalmente alterar le curso del processo atherosclerotic experimental. Iste factores es de importantia in le prophylaxe e le therapia in tanto que illos reduce e retarda le disveloppamento de atherosclerosis. Le effectos in question pote esser considerate como utile in varie grados in le prevention de atherosclerosis etiam in humanos.

Ab iste puncto de vista nos ascribe importantia special a acido ascorbic.

Tamen, il ha nulle dubita que factores de action negative—i.e. influentias capace a intensificar le processo atherosclerotic—es etiam presente e capace a exercer un rolo significative. Ab le puncto de vista del medicina preventive, certe mesuras deberea esser evitate pro eliminar tal influentias adverse.

A parte le question del influentia active super le processo atherosclerotic in le vasos, on debe rememorar se que il es possibile afficer le stato del histos que suffre le plus durante le disveloppamento de atherosclerosis, i.e. notabilemente le myocardio. Nostre recercas ha demonstrate que factor representate per le concentration de cholesterol—o, plus specificamente, le grado de disveloppamento del atherosclerosis—non es le sol determinante del disordine functional e structural del myocardio, ben que illo es certo un factor principal in iste disordine. Alte importantia—in le disveloppamento de pathologia myocardial in le presentia de atherosclerosis—es a attribuer a adverse factores supplementari como per exemplo excesso de exercitio physic e anoxia.

Es presentate un numero de illustrationes que signala le possibilitate de influentiar le disveloppamento de atherosclerosis experimental per un via purmente nerval, i.e. per le application de agentes pharmacologic que affice le partes superior del systema nervose central. Si il esseva possibile—ben que solmente de maniera approximative—correlationar le presente constatationes con observationes clinic, il sequerea que excessos de excitation e de stimulation resulta in effectos adverse, i.e. in le intensification e acceleration del disveloppamento de atherosclerosis, durante que un reduction del excitabilitate del componentes superior del systema nervose central, i.e. un stato de inhibition, produce effectos favorabile in le senso que illo retarda o reduce le disveloppamento de atherosclerosis.

Glenn, F., and Dineen, P.: Recurrent Mitral Stenosis: A Case Report. Ann. Surg. **143:** 405 (Mar.), 1956

A report is presented by the authors of a patient who had 2 commissurotomies for the treatment of mitral stenosis. Subsequently the patient died, and an autopsy was performed. It was found that the process of recurrence of the stenosis of the mitral valve following commissurotomy was not a closure of the operative fracture but rather a progression of the rheumatic disease. Microscopic examination of the heart demonstrated evidence of a smoldering rheumatic myocarditis and valvulitis.

ABRAMSON

PANEL DISCUSSION

GUEST EDITOR: LOUIS N. KATZ, M.D.

Rehabilitation of the Cardiac Patient

By LOUIS N. KATZ, M.D., ROBERT A. BRUCE, M.D., NORMAN PLUMMER, M.D., AND HERMAN K. HELLERSTEIN, M.D.

MODERATOR LOUIS N. KATZ (*Chicago, Ill.*): Before I call upon my colleagues I wish to make a few introductory remarks. We as physicians must view heart disease in all its ramifications. Heart disease is primarily a chronic process. The problem is more than the immediate alleviation of acute exacerbations of the disease, involving a temporary sojourn in the acute hospital, or its equivalent at home. The management of the acute phases of heart disease is so exciting to the layman, medical student, house officer, and headline writer—and, unfortunately, to some physicians—that the chronic nature of this disease may be overlooked.

Care is required for the patient over months and years, care in which proper small things constantly repeated, surprisingly, have a great cumulative effect. In the last analysis, proper care means prevention of recurrences and ultimately of going to the normal population and preventing the disease from occurring in the first place.

However, it is not enough merely to stop the advance of disease. One must endeavor to restore the patient to the full life. This is rehabilitation. This philosophy should be the credo of all physicians and of all the ancillary professionals dealing with a cardiac patient incapacitated by his disease. Man is a complex creature with a mind and emotions, and illness affects him in his totality—mind and body besides heart and blood vessels.

You are all aware of iatrogenic heart disease in which the physician and the ancillary aid, by indiscreet or thoughtless remarks or actions, creates some of the manifestations of heart disease that are not organically present. Moreover, the patient with heart disease can also have his organic difficulties multiplied in the same way iatrogenically. Consequently, in rehabilitation one has to deal not only with the physical disability but with the mental and emotional attitudes of the patient, of his family, and even of the society in which he lives.

Rehabilitation to be effective must be complete. It must attempt to attack all aspects of the situation. It must represent an appreciation of the machinery that is deranged in the human body, of the recuperative powers of living things, and of the limits of the stresses that can be imposed. But it involves more than this. It involves an expert analysis of the patient's mental attitude to his disease, the unraveling of the hidden fears that reside in him and his family. It requires the instillation of hope that he will attain within the limits of his body—and more than he expects—his birthright to happiness of the full life and gainful occupation in a job that is interesting and challenging.

There is therefore need for vocational evaluation and guidance. Proper rehabilitation rests upon the tripod of (1) the sympathetic, psychosomatically oriented, and scientifically trained cardiologist; (2) the kindly, psychiatrically trained medical social worker, and (3) the mature vocational counsellor. These 3 operating as a team, with the physician as their leader, in a society that recognizes that work is as much the fashion as birth, death,

A panel discussion on the rehabilitation of the cardiac patient was conducted in conjunction with the Scientific Session on Clinical Cardiology, at Music Hall Auditorium, Cincinnati, Ohio, on Monday morning, October 29, 1956.

; ıd taxes, will bring into proper balance the ; mewhat one-sided approach to cardiovascu- r disease practiced by many, with its over- mphasis on the acute dramatic phases and ieir spectacular alteration by therapy. It ill lead to the addition to ordinary manage- ıent of preventive medicine and rehabilita- ion in equal proportions.

We are just at the beginnings of a science f rehabilitation. The day must soon come hen no alert community can neglect this im- ortant area, when no medical center is con- idered to be really a center unless it has an dequate rehabilitation program, and when his program reaches into every home, rich and poor alike. It will then be accepted that in treatment we do not stop by merely making people well, but well and useful.

We must stress as the aim of good medicine, the restoration of human beings to their nor- mal role in the family, in their society, and at their work. This is no investment in bricks and mortar; it is an investment in human beings.

The beginnings of the science of rehabilita- tion have been made and the results already have been brilliant, exciting, and with great promise of better things to come. The field is already sufficiently advanced so that we may apply to rehabilitation the credo of the Heart Association: "There is hope for you and your heart through service, education, and research." But beginnings are not enough. We must expand our program of rehabilita- tion by creating more facilities, by educating everyone to its needs, and by supporting re- search to unravel the interrelationships of the emotions and the body machinery at work.

It was because I felt these things so sincerely that I accepted Dr. Harold Feil's invitation to moderate this symposium and to make these few introductory remarks.

I now will call on the panelists who will out- line in the remaining time some particulars on rehabilitation. First I will call on Dr. Robert A. Bruce.

DR. ROBERT A. BRUCE *(Seattle, Wash.)*: Fellow students of heart disease, I would like to suggest that effective rehabilitation of cardiac patients depends upon the favorable balance between physiologic capacity and energy requirements of the work load. Let us examine each of these areas briefly.

Energy requirement may be assessed from the approximate rate of oxygen consumed in the performance of the task and from the duration of effort. Although other character- istics are informative, the simplest measure of intensity of effort is the percentage ratio of oxygen consumption at work to its value at rest (fig. 1). This ratio fluctuates with work requirements and increases with peak loads to higher levels. The magnitude and frequency of these peak loads are also important. You will note that I have taken the value 400 per cent, which will refer to the stress test I am going to talk about later. A peak load is also depicted that is more nearly comparable to Dr. Master's 2-step test.

Examples of the approximate energy re- quirements of some ordinary daily activities indicates that these may be placed within broad categories representing slight, moderate, severe, and very severe work.[1-3] Thus sitting, standing, talking, represent only slight physi- cal activity, whereas walking slowly on a level, requires an appreciable but moderate expendi- ture. Walking on either loam or snow, or walking upgrade, such as hill climbing, can be very severe work (fig. 1).

Similar measurements of energy require- ments of common jobs in an aircraft industry in Los Angeles have been made available to me.[3] Since much of the work is more or less mechanized, the energy expenditure for the particular job sampled does not seem to repre- sent very severe work.

In like manner the energy requirements on the farm represent corresponding ranges for mechanized tasks, plus much higher energy requirement for certain manual tasks and chores. These do not take into account en- vironmental heat stresses, which often occur.

The relative variance of 2 different indus- trial jobs of a highly repetitive character has been studied. On the basis of a large number

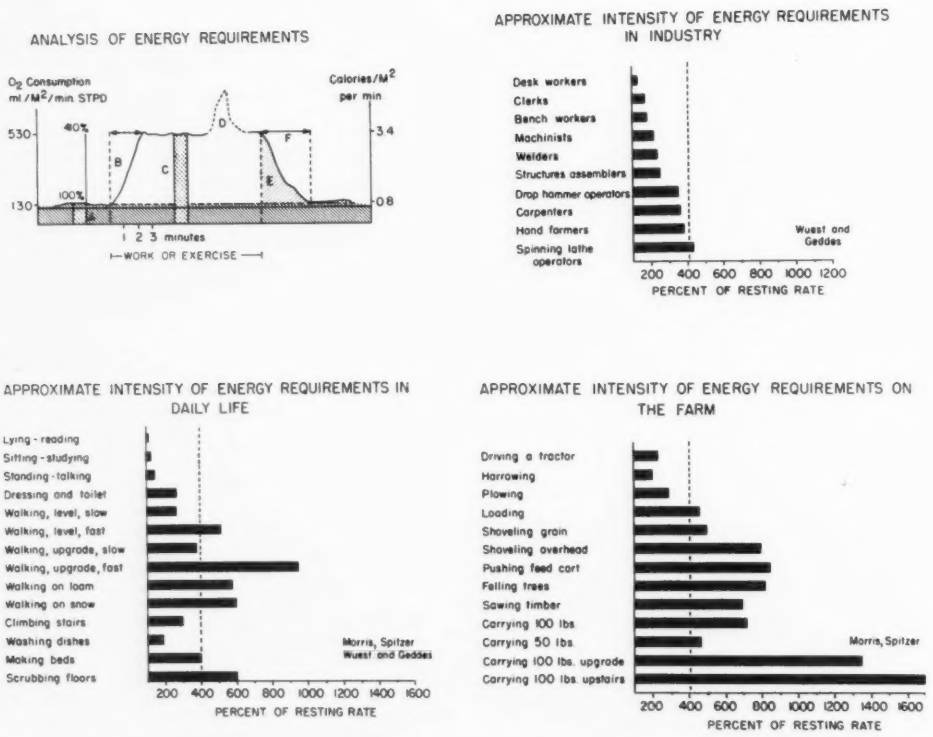

FIG. 1. Analysis of energy requirements by means of graphic recording of oxygen consumption. *A*, requirement at rest; *B*, lag in increase of oxygen consumption with work or exercise; *C*, average value per minute during a steady state of physical activity; *D*, further increment with peak load; *E*, oxygen debt; and *F*, time lag for recovery. The approximate intensity of energy requirements for representative activities in daily life, industrial jobs and work on the farm are expressed as percentages of resting requirement, corresponding to value *C*.

of tests on these noncardiac workers, "other factors" accounted for more of the variability than the relative importance of day-to-day variations in the same men, or man-to-man variations on the same day.

Furthermore, Wuest, Geddes, and Enterline[3] did not find any significant difference in the energy requirements for noncardiac and cardiac employees performing the same industrial jobs. It is significant from the standpoint of job placement of cardiac patients that they probably do not have higher requirements than noncardiac subjects when performing the same task.

Now let us direct our attention to criteria for the evaluation of physiologic capacity for work.

Physiologic capacity of the cardiac patient fluctuates with both the natural history of disease and the effects of medical treatment. Clinically, physicians have used several criteria for determining whether work requirements exceed capacity of cardiac employees. Thus a history of symptoms on the job, such as fatigue, dyspnea, or pain, are helpful but not specific. Additional criteria are the worker's recognition of the lack of tolerance to recreational activities in addition to work, the needs for shorter hours of work or more rest, and medical treatment.

Unless there are signs of pulmonary congestion, venous engorgement, or cardiac edema, the physical examination provides little insight into the possibility that the worker is overtaxing himself.

In the experimental clinical laboratory, symptoms and signs developing in response to a suitable stress may be helpful to test cardiac reserve capacity.[4] The energy requirement should be increased about 400 per cent by an appropriate form of effort that involves large muscle masses, requires no training, and can be effectively standardized. Walking slowly at 1.7 miles per hour on a 10 per cent grade of incline on a motor-driven treadmill ergometer achieves these goals. Numbers of measurements may be made with a high degree of reproducibility. This does not necessarily determine whether any cardiac patient works in excess of his capacity, but it is helpful to determine whether tolerance of this level of exercise is impaired, since the majority of employees appear to have work requirements—except for peak loads—within this range. Under these arbitrary conditions, normal tolerance for exercise in an ambulatory subject may be defined as the ability to perform such an effort of walking for 10 minutes without symptoms, signs, or physiologic impairment, and with complete and rapid recovery within 3 to 5 minutes. Time is not available for an extensive discussion of important precautions and limitations of this test that have been presented elsewhere.[4] However, I do want to emphasize that at the time the test is performed, it is essential that a physician be in attendance, and stop the test whenever symptoms of cerebral anoxemia or ventricular tachycardia are shown.

Results of this test have been compared with the opinions of a group of cardiologists, under the direction of Dr. Sparkman, who examine patients referred to the Northwest Cardiac Work Evaluation Clinic.[5, 6] In patients with either coronary artery or rheumatic valvular disease, dyspnea and fatigue were commonly encountered with this exercise test (fig. 2). Coronary patients more often developed chest pain. The most important sign was the inability to continue this exertion for 10 minutes. Forty-five per cent of the patients were unable to walk for 10 minutes, and from 5 to 15 per cent were unable to walk for as long as 3 minutes at this particular standardized work load. Another sign was the inability to raise the systolic blood pressure, or an actual fall in its level. Patients rarely show evidence of congestion, which disappears promptly within 4 or 5 minutes. The changes in the precordial electrocardiogram taken throughout the test are also important.

Based upon a modification of the fitness test developed at the Harvard Fatigue Laboratory several years ago, an index of physical fitness (PFI) has been utilized to express the cardiorespiratory performance.[7] In this sense, fitness varies directly with duration of effort, efficiency of oxygen uptake in relation to ventilation, and inversely with cumulative heart rate for 3 minutes of recovery. Normal values range from 13 to 26. The relationships of exercise tolerance, to distribution according to etiology and functional capacity of 127 patients appraised by this clinic are shown.

Most of these patients were in classes II and III of functional capacity. The mean PFI for class I rheumatic patients was higher than that for class I coronary patients, probably because of the 25-year difference in mean age between the 2 groups. Although the mean PFI decreased progressively from classes I to IV, there was marked variation within each of these groups. Thus the exact value obtained is of limited value in comparing one individual with another, but of considerable value in comparing the results obtained serially in the same patient over a period of time.

The relationship between the subjective appraisal of functional capacity and the objective test of exercise tolerance has shown satisfactory agreement in 85 per cent of the rheumatic and 70 per cent of the coronary patients. The chief cause of discrepancies was found to be an unsatisfactory history, followed by occasional examples of excessive

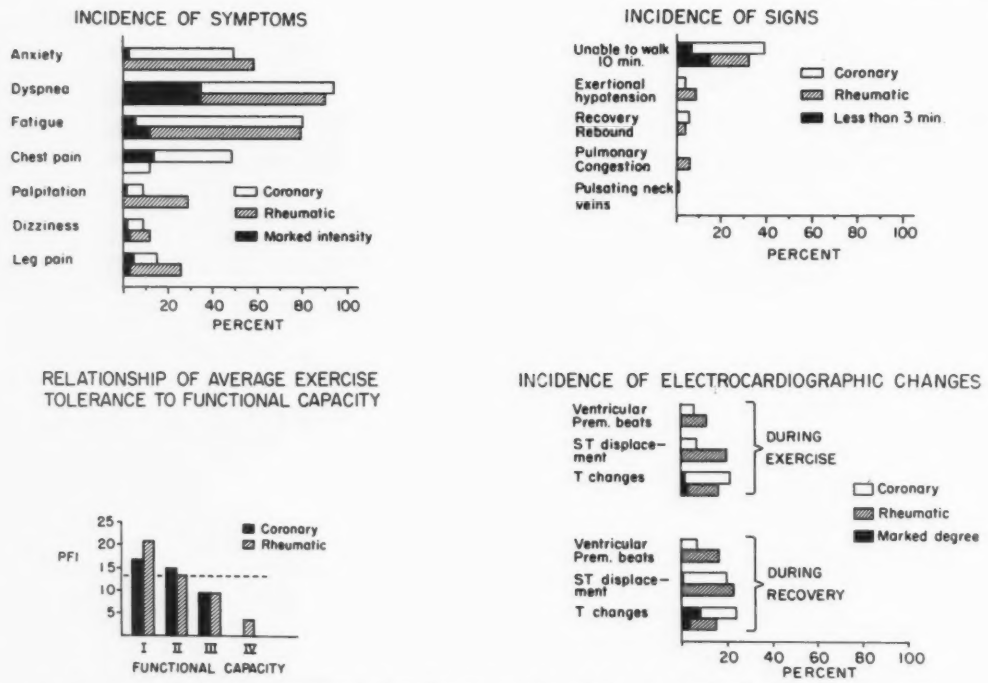

FIG. 2. Analysis of performance of cardiac patients in relation to standardized work load corresponding to value *C* in figure 1. The frequency of symptoms, signs, and electrocardiographic changes are presented as averages for patients with either coronary or rheumatic heart disease. Solid bars, *marked intensity*, indicate incidence of symptoms severe enough to stop the exercise before completion of the 10-minute period. The relationships between functional capacity, (N. Y. Heart Association), and exercise tolerance (PFI) are also shown for patients in these 2 etiologic groups.

limitation of physical activity either by patient or physician, recent convalescence, or other disease.

A not infrequent incidental by-product of the test procedure has been the reassurance of the patient who did not appreciate he could expend as much energy with little discomfort and no harm to himself. Another important by-product was the opportunity to demonstrate mechanisms of impairment, and permit the physician to advise the patient of his limitations in relation to symptoms. None experienced any significant untoward effect; all were carefully supervised by a physician in attendance. Fortunately the procedure rarely discouraged patients from returning for follow-up tests whenever requested.

Recently we have been determining the cardiac output at rest while the patient sits in a chair, and again during a steady state of exercise while walking on a treadmill. This is done by means of the dye-dilution technic, with an ear oximeter and Wiederhielm's direct-recording amplifier system with linear characteristics. Although 4 venipunctures are required, the necessity of either cardiac catheterization or arterial sampling is avoided. These data, together with oxygen consumption, heart rate, surface area, and hemoglobin concentration permit a graphic analysis by Rushmer's diagrams of the relationship of changes in oxygen consumption to blood flow, arteriovenous oxygen difference, and venous oxygen reserve.[8] Cardiac reserve can be analyzed in terms of changes in stroke index and heart rate.

It is too early to judge the ultimate value of such studies and obviously much more research is needed. Nevertheless from the preliminary experience accrued thus far, some form of objective evaluation of cardiac reserve is helpful in guiding the physician. Then the work prescription for the cardiac patient to be rehabilitated can be formulated in relation to both the energy requirements of the job and the functional capacity of the employee.

MODERATOR KATZ: Thank you, Dr. Bruce. I think all will agree with me that this is a beautiful demonstration of the utilization of basic scientific knowledge in an area of community service.

The next participant in the symposium will be Dr. Norman Plummer.

DR. NORMAN PLUMMER *(New York, N.Y.)*: Dr. Katz, ladies and gentlemen, I shall discuss this problem today from the angle of the industrial physician. At a similar panel a year ago, Dr. Paul D. White stated: "I would like to emphasize the beneficial effect of work on body, mind, and soul in any occupation in which it is possible for a cardiac patient to engage. Idleness breeds unhappiness and is actually bad for the health. It is a rare patient indeed who is fit for nothing. It greatly pays to make every effort to find something, either vocational, or avocational, into which to fit the sick man or woman."

I am in full accord with Dr. White and think that an important part of the recovery from heart disease is the provision that the individual be occupied, and that in most instances this means that he should resume gainful employment. It is almost generally accepted today that cardiac patients want to work, that they can work and when properly placed, can work productively and without harm to themselves or to others.

That seems to make the employment of cardiac patients a simple procedure, particularly considering today's labor market where there are more jobs than people to fill them, and the further fact that in this machine age work is light and hours are short, both just right for the cardiac patient. Despite these facts, the employment of cardiac subjects (and other disabled workers) can often be a serious and perplexing problem.

Why should this be? Primarily it is because of what today is called interpersonal relationships. The employment of a cardiac patient often involves many complicated relationships between many different people, groups of people, and agencies, all approaching the problem with somewhat different attitudes and from different angles. Involved in a single cardiac case there is the employee, the employer or potential employer, the employee's family, his private physician and perhaps a specialist, a clinic, a social worker, and sometimes the local Heart Association, the union, the Workmen's Compensation Board, and finally, particularly if it becomes a compensation case, maybe 2 or 3 lawyers.

Do all of these people and agencies accept the principle that the cardiac patient wants to work, can work, and when placed properly, can work productively and without harm to himself? Maybe they do, but from my experience they do so with many qualifications.

Let us, for a moment, think in terms of some of the individuals involved in these interpersonal relationships. First, let us consider the cardiac employee. Let me emphasize at the start that there are millions of cardiac patients working effectively and continuously at productive jobs with great satisfaction to themselves as well as to their employers. On the other hand, many of them do not work effectively, when returning to work, or when given jobs. They may have been frequently absent, may be unreasonable in their requests for restricted duties, and when their disease progresses they may blame it on their job. Some individuals want the additional income that comes from employment but they desire—and many times this, I am sure, is in their subconscious mind—the leisure and the restricted activities of retirement. Usually, it is a psychologic reaction rather than organic heart involvement itself that results in the failure

of the cardiac patient to perform his job effectively.

Next, let us consider the employer. The crusade for the employment of the disabled naturally is directed primarily at employers. Many times the problems encountered by the employer are not accepted sympathetically. To be realistic we must recognize that the employer of these persons has some real risks and liabilities. The risks are mainly financial, such as the cost of increased absence and increased replacement, increased number of restricted assignments, and increased insurance and compensation rates. In one way or another large companies can absorb these extra costs. However, the small employer, and most employment is by the small employer, cannot. Therefore, most small employers do not employ cardiac patients knowingly, although, because they are small, they do not have the facilities for identifying and rejecting cardiac subjects when they are taking on new employees.

This difference between the large and the small employer is important. Almost all large companies have large numbers of cardiac employees on their payroll, although as a rule, they are methodical in rejecting applicants who have heart disease, considering that they are already carrying their responsibility by retaining those employees who develop heart disease while working for them.

In employing cardiac workers, proper placement is most important, not only for the employee, but in reducing the risks to the company. Most large employers, and some of the smaller ones, are doing an excellent job in this important activity of work classification and job placement. Dr. Hellerstein will cover this phase in his presentation. Many employers are deriving great satisfaction from employing the disabled. By doing this they find that they are hiring or retaining people who have acquired extra skills, aptitudes, and long experience. However, with few exceptions, good employees do not become better employees, because of an acquired disability such as heart disease. Our reasoning on this often becomes distorted. It is true that the stable, reliable employee with heart disease is, as a rule, more valuable than the unstable, unreliable employee without physical disability. However, we should bear in mind that there are extra problems and costs involved in hiring the handicapped. It can be said that most employers, certainly the larger employers, are accepting the cost problems and responsibilities of employing cardiac patients more and more. However, in doing so, they have 2 other necessary interpersonal relationships that often disturb them. One is the relationship with the private physician and the other with the Workmen's Compensation Board, which often means relationship, as I mentioned before, with members of the legal profession.

Let us consider the employee's private physician. From the angle of those of us in industry, this is a most important relationship.

As a rule, a cardiac employee's attitude toward his job is strongly influenced by his private physician or cardiologist. When an employee having had a mild coronary, returns to work at the end of a year, i.e., at the end of his sickness benefits, instead of at the end of 2 or 3 months, i.e., the usually optimum time, it is his physician who has helped to develop this plan. When the employee is in his sixties, with a badly damaged heart, really desiring and needing to retire, and insists on returning to work again, it is the private physician with whom he is closely allied who is responsible. The cardiac worker who is overcautious and overconcerned, so that he is unable to work continuously and effectively, often derives this attitude from his private physician. In the case of the employee who develops heart disease or has a relapse and then in a remote and unreasonable way relates it to his job, it is usually his private physician who opens this claim as a workman's compensation case.

Just as it is the minority of cardiac employees who work ineffectively, so it is the minority of doctors who create many of these problems in the employment of the disabled.

We must salute the vast majority of doctors who are properly oriented for so tremendous a service in encouraging cardiac patients to work. The medical profession nevertheless has much to do in terms of educating all physicians in the proper knowledge of heart disease, the understanding of human nature, and of jobs—all essential in order to carry out this most important phase of treatment.

Finally, let us briefly consider insurance and Workmen's Compensation. Here is an important sphere of activity of the American Heart Association.

For many years members of the Heart Association have appreciated that both the application of Workmen's Compensation Laws and the application of industrial insurance has had a tendency to penalize the employer of cardiac patients and in turn, to create obstacles to their employment or re-employment. Several years ago a committee known as the Committee on the Effect of Strain and Trauma on the Heart and Great Vessels, with Dr. Paul D. White as chairman, was appointed. About a year ago, Dr. White was authorized to appoint 2 subcommittees, one called the Clinical Pathological Subcommittee and the other the Medical, Legal, Insurance and Industrial Subcommittee. Both of these subcommittees during the past year were authorized to set up study groups with research associates reporting to responsible investigators who are members of the parent committee. The Clinical Pathological Subcommittee is evaluating the clinical and pathologic evidence that exists on the effect of trauma, strain, and stress on heart disease. The Medical Legal Subcommittee of which Mr. Barnett S. Fox and I are the responsible investigators, has a study group with Mr. Henry D. Sayer, former industrial commissioner of New York as full time research associate, compiling, analyzing, and evaluating Compensation Laws and court decisions as they relate to cardiovascular disease.

Also, Mr. Sayer and his staff are carrying out a survey in the insurance and industrial organization to ascertain and evaluate obstacles that exist in employing cardiac workers, particularly those that may arise from the application of insurance plans and Workmen's Compensation. I can report progress and can tell you that valuable reports from those 2 study groups will appear. The subcommittees are planning to use the findings as a basis for recommendations to the Heart Association.

In conclusion I would say that there are a number of obstacles to the employment of cardiac patients but a better understanding of this entire problem will lead to a much better future for the cardiac worker in industry.

MODERATOR KATZ: Thank you, Dr. Plummer. You have made it clear that it is not just numbers and machinery. It is a problem of integration in a complex society of private enterprise.

The subject will be continued by Dr. Herman K. Hellerstein.

DR. HERMAN K. HELLERSTEIN *(Cleveland, Ohio)*: My pleasure and task is to discuss the Work Classification Clinic. Since the original unit was founded by Dr. Leonard Goldwater at the New York Bellevue Hospital in 1941, 42 similar units have been established and supported by the American Heart Association. Certainly today is an appropriate occasion to re-evaluate the work classification concept and to discuss the accomplishments, limitations, and experiences of various clinics throughout the United States. I am grateful to the directors of the Work Classification Clinics in New York, Boston, Philadelphia, Iowa, Seattle, and elsewhere, for providing data.

The accomplishments of the Work Classification Clinic can be divided into 3 categories: (1) service to patients, (2) education, and (3) potential and realized research value.

The Work Classification Clinic may play an important role in returning the cardiac patient to work. After a patient with heart disease has recovered from his acute illness, return to work is usually indicated, but in actual practice is often very difficult. The basic problem is to determine and to match

the patient's total capacity with the demands of a specific job. This cannot be solved by prescribing a "light job." Because the total problem is complex, a team approach is often required, in order to integrate and to concentrate the knowledge of multiple disciplines for the benefit of the individual patient.

The clinic team of the Work Classification Clinic generally consists of a cardiologist, vocational counselor, medical or psychiatric social worker, and occasionally a psychiatrist. The social worker plays a key role in evaluating the patient's pre-illness personality and temperament, attitudes, meaning of the illness to the patient, his intellectual and emotional understanding of his disease, his family and economic problems, and the emotional milieu of a job.

The vocational counselor obtains detailed information as to the work history, the subject's skills, education, work attitude, personality needs and work motivation, job features (skills, effort, responsibility, and working conditions), transportation problems, and exact details of the present or past employment.

The cardiologist evaluates cardiac function as well as structural changes and recognizes the importance of placing emphasis upon the function of surviving tissue. In addition to a complete medical history and physical examination, chest fluoroscopy, routine blood analysis, and exercise tolerance tests are performed. In the Cleveland experience Master's 2-step test has been performed in all but a few cases and the treadmill test of Bruce in approximately 100 cases.

After the studies are completed, the clinic team confers to present, discuss, and integrate the findings. The total energy requirements (work, basal, recreational) are estimated and related to the patient's response to exercise tests of known energy requirements (Bruce's test, 5 to 6 calories, Master's 2-step test, 7 to 8 calories),[9] and to life activities, (walking, stair climbing, shaving, showering, gardening, etc.) whose energy requirements have been measured.[10]

A detailed practical work recommendation is made and forwarded to the patient's private and industrial physician. Personal communication with placement agencies, rehabilitation services, the employer, personnel manager, union steward, etc., may be necessary to implement the recommendations. The patients are re-evaluated every 3 to 6 months during the first year, and at 6 to 12-month intervals thereafter.

The results of this multidisciplinary approach have been remarkably similar throughout the country.

The source of referral of patients has depended upon the original orientation of the clinic in specific communities. In Philadelphia the main source has been the industrial physician, in Cleveland and other communities the source has been predominantly the private physician. The characteristics of the clinic population have been similar: 90 per cent are male; 90 per cent are white; from 50 to 75 per cent are in the age group from 35 to 54 years, which is usually the most productive phase of life. In 46 to 63 per cent of the patients the emotional impact of the illness on the patient has been as important as the organic heart disease itself in determining employability.[11, 12]

The etiologic types of heart disease were representative of clinical heart disease in mid-twentieth century America; 20 per cent rheumatic heart disease, 12 per cent hypertensive cardiovascular disease, 47 per cent arteriosclerotic heart disease with or without hypertension, 8 per cent no discernible heart disease; and the remainder included cor pulmonale, syphilis, congenital, and unknown heart disease.

In every clinic experience the employment status has improved. The number employed at the initial visit (approximately 30 to 40 per cent) has increased to 50 to 75 per cent at follow up visits. This is a substantial accomplishment! The occupational status has also shown a consistent change. A remarkably high percentage of the patients, 70 to 94 per cent, were able to remain in the same job category with little or no modification.

TABLE 1.—*Jobs Held by Work Classification Clinic Patients with Heart Disease*

Clerical	Semi-Skilled
accountant	assembler, motor
auditor	box maker
bookkeeper	burrer
general clerk	braker machine
government clerk	centerless grinder
main clerk	fitter
mail sorter	glass maker
office clerk	hand lathe, automatic
order filler	instrument man
police stenographer	mixing machine
secretary	operator
shipping clerk	packer
stock clerk	painter
timekeeper	photostat
tool clerk	pipe threader
Managerial and Official	plumber
bakery	pump man
barber	punch press
contractor, building	solderer
contractor, floor	spindle drill
dispatcher	stamper
executive assistant	tool and die maker
foreman	valve tester
inspector	vertical turret lathe
retail food	water treater
Salesman	welder
automobile	Unskilled
clothing	day worker
hardware	foundry worker
insurance	laborer
printing	material handler
refreshment	pipe layer helper
tobacco	plumber helper
vending machine	Service
Professional	bar tender
dentist	domestic
engineer	elevator operator
nurse	fireman
physician	messenger
social worker	porter
	tool crib attendant
	truck driver
	watchman

Table 1 illustrates the wide variety of jobs successfully held by the cardiac patient, and invalidates the concept of a "cardiac job." Whenever possible the patient was advised to remain and usually was able to remain in the same industrial plant and in the same industrial and occupational classification. Downgrading as a result of heart disease has occurred in only 5 to 7 per cent of all cases.

Effect of Occupation on the Medical Status. There has been no evidence that the prescribed work has aggravated the course of heart disease of our patients. As of April 3, in Cleveland, no medical legal compensation claim has been made by any of our 1,100 patients over a period of 6 years. A very surprising and gratifying observation has been the fact that the patients improved while working. Dr. David Gelfand of the Philadelphia Work Classification Unit has reported that 55 per cent of the patients with rheumatic heart disease, 76 per cent of those with hypertension, and 65 per cent of those with coronary artery disease were medically improved or unchanged while working. Our experience in Cleveland has been similar. The fact that the cardiac and occupational statuses improved in the employed cardiac subjects and that approximately 75 per cent of all patients studied at the Work Classification Clinic were working at a follow-up visit must be recalled in the evaluation of certain heart operations that claim to be successful because a similar number of patients are employed after operations.

Summary of the Service Accomplishments. Through the employment of a team consisting of a medical social worker, vocational counselor, and cardiologist, and through the use of clinical methods of evaluation, about 75 per cent of the patients with heart disease have been able to return to competitive industry in a great variety of jobs, without evidence of harm to the patient, his fellow worker, or employer. These jobs have provided status, self-esteem, and substantial remuneration. The educational value has been great also. We physicians have learned much about the contributions of other disciplines and about the course of heart disease. Over 200 physicians have participated in the functioning of the Work Classification Clinic in Cleveland. The clinic has been used to demonstrate to medical students a holistic approach to the patient.

In each community the Work Classification Clinic has focused attention upon the problem

of employment of the cardiac patient, and has demonstrated to management, labor, insurance carriers, physicians, and even legislators the value of the cardiac employee. In each locale the success of the Work Classification Clinic has encouraged the private and industrial physicians to be less fearful in advising employment for their cardiac patients. This encouragement has been similar to, but not as dramatic as that which Dr. Paul D. White gave to the medical profession and to cardiac patients throughout the world by the way in which he managed the rehabilitation of a famous patient.

The greatest accomplishment, however, is not in the service rendered, but rather the demonstration for the need for research in certain areas. One of the most striking needs is the prevention of invalidism. The physician, unwittingly or otherwise, plays an important role in the genesis of this invalidism.[11] Since it is now established beyond a doubt that a patient with heart disease can work, the need for preventing iatrogenic invalidism becomes even more cogent.

One of the most important and difficult tasks in work classification is the estimation of the stress of a job and the capacity of the cardiac patient to meet it. I think the success of the various clinics may be attributed to good clinical judgment and intuition, the humanity and more optimistic philosophy that prevails today regarding the cardiac patient, and in greater part, I believe, their success is due to the fact that most jobs do not require much energy, and that cardiac patients have the capacity for such an expenditure.

Clinical tests to measure the cardiac patient's capacity to work have been valuable when interpreted properly. The response to Bruce's treadmill test or Master's 2-step test with an average load of 4 and 8 calories respectively[9] must be related to the requirements of a specific job. Had we used Bruce's index of fitness alone as a criterion of employability, most of our class II and class III patients would not be working. There have been many discrepancies between this index of fitness and employability. For example, one patient with an index of 23.3 was not employable, while another with an index of 6.3 was employable. The determining factor was the availability of a job where energy requirements were less than that of the individual's capacity.

In the Cleveland Work Classification Clinic, we have referred generously to published data of Passmore and Durnin[10] and others, in order to estimate the caloric requirements of various jobs. However, more information about current job requirements in contemporary America is needed. In the past 2 years, Dr. Amasa B. Ford and I have measured the caloric requirements of specific jobs in Cleveland industry. Sixty-seven subjects, including cardiac subjects and matched controls, were studied on the job. The workers included supervisors, machine operators, firemen, clerks, and service personnel. There was no statistical difference in the energy expenditure of the cardiac patient and the controls: at rest 1.30 calories per minute, S.D. 0.25, peak activity 3.04 calories per minute, S.D. 1.07, average during the entire shift 1.97 calories per minute, S.D. 0.48, and average expenditure during actual work was 2.29 calories per minute, S.D. 0.64. The minute ventilation of the cardiac subject and the controls was similar: at rest 8.74 L. per minute, S.D. 2.0 L. and during peak activity 16.9 L. per minute, S.D. 4.8. During the customary pauses and breaks of the working day, the various parameters of cardiovascular function returned toward control values.

The pattern of energy expenditure has often been more important than the magnitude. In one illustrative case, a boiler fireman expended from 1.34 to 6.2 calories per minute. This was one of the heaviest jobs we evaluated. However, for 247 minutes of the day, the subject expended 1.34 calories, during resting and watching of controls; 3.9 calories for 246 minutes while using control devices, and mixing ingredients, and for 17 minutes, 6.2 calories were required during the shoveling and removal of ashes.

The frequency of rest periods, pauses, and

relief of boredom influenced the performance during the working day. Variations in the energy requirements of the same task depended more on the basis of the personality needs of the worker than on the energy requirements of the job.

The effort required by these representative jobs (which admittedly excluded foundry workers, dock hands, etc.) is surprisingly small, and not significantly greater than that required by ordinary home activities. The average housewife expends more energy than her working mate, when she irons clothes (4.2 calories per minute), makes a bed (5.4 calories per minute), cleans windows (3.7 calories per minute), or peels potatoes (2.9 calories per minute).[10] Little wonder that the male cardiac patient is so anxious to flee the home to return to his job!

Perhaps the most significant contribution of the Work Classification Clinic is the demonstration of the need of the following types of research:

1. To expand the science of ergometry: to determine the energy requirements of a wider range of occupations; to measure the changes in the physiologic costs with changes in work methods; to develop methods of job simplification; to study the phenomenon of fatigue.

2. To study the effects of underexertion (undereffort) as well as overexertion.

Since recent reports seem to indicate that physical fitness enhances survival in coronary occlusion, the deleterious effects of overautomation, oversimplification of jobs, boredom, and of restriction of the worker should be evaluated. In fact the effects of a program of physical fitness on work performance and on the course of heart disease should be studied systematically.

Conclusions. The experience of the Work Classification Clinic has demonstrated that cardiac patients are employable in a great variety of jobs, safely and productively, and clarifies the urgent need for basic research in ergometry, human physiology, and psychiatry to enhance the return of the patient with heart disease to the world of work.

MODERATOR KATZ: Thank you, Dr. Hellerstein. You have made your presentation clearly and I am sure we now have a better understanding of the function of the Work Classification Clinic.

We now come to the period of discussion. I would like to ask Dr. Plummer to tell us whether he agrees with everything said by his fellow panelists.

DR. PLUMMER: Dr. Katz, I can't say that I agree with everything that has been said. In the first place, I think Dr. Hellerstein's figures that show that work on the job requires less energy than the work done at home, should be confiscated. If these figures get to our women folk we shall be in trouble. Here is a question for you, Dr. Katz. Don't you think we should do something about that?

MODERATOR KATZ: No, we shouldn't because ours is a society dominated by women, and after all, the male is the weaker sex!

DR. PLUMMER: I am impressed with the physiologic tests described, but I do have a question that I would like to ask the other 2 members of the panel. Would Dr. Bruce and Dr. Hellerstein tell us how they believe this testing can actually be used in industry and whether this type of testing has some value in our medical departments in industry?

DR. BRUCE: The use of the treadmill is to standardize the exertion and to minimize the varieties. If we did no more than get employees to walk and time how far or how long they can walk, up to 10 minutes, it would not be difficult to derive useful and practical information.

DR. HELLERSTEIN: I don't think it is necessary for industry to study each employee on a treadmill in the plant's dispensary. There are simpler methods of estimating fitness. The industrial physician can make on-the-job observations in specific cases. However, I would like to emphasize that it is the responsibility of industry to determine whether a subject can or cannot fulfill certain jobs. It is unrealistic to assume that a young or apparently healthy older worker can withstand the stresses of certain high energy jobs.

MODERATOR KATZ: The answer is yes, but the tests need not be as elaborate as those employed in research.

DR. BRUCE: I would like to direct one question to Dr. Plummer. Would he be a little more specific about his own experience as to how often the cardiac patient who returned to work in his own industry presented real problems to management?

DR. PLUMMER: Dr. Bruce, I cannot give any percentages but certainly it is an every day occurrence that there are problems in getting a cardiac patient back on the job. We spend a great deal of time talking over these problems with the private physician. We find that the psychological factors for the most part are much more important than the physical factors. Occasionally we deal with a problematic case; the most problematic case is the one that gets over into compensation. I would like to ask you the question, whether anyone has ever measured energy requirements of extracurricular activities, as for example, at a compensation hearing. I have an idea that the doctor's blood pressure and his energy expenditure sometimes would go even higher than that of the employee or his counsel.

MODERATOR KATZ: Does that require an answer or was that simply a question used to make a statement?

DR. PLUMMER: Well, Dr. Katz, it can be either way.

DR. BRUCE: I have no data on that particular point.

MODERATOR KATZ: Thank you both. And lastly, Dr. Hellerstein, do you disassociate yourself from your colleagues in any fashion, or have they stated the case fairly?

DR. HELLERSTEIN: I think they stated part of the case, i.e., all industrial physicians are not so enlightened as Dr. Plummer. Most industrial physicians are not heart surgeons.

MODERATOR KATZ: We must get other industrial physicians to take up cardiac surgery.

Dr. Feil has just informed me that our time is up. Time has a habit of passing too rapidly. I am sure that there are many things still unsaid but what has been said should give all of us plenty of food for thought. May I thank my panel associates for excellent presentations and the audience for listening so courteously.

REFERENCES

1. SPITZER, I. H.: The energy requirements of physical work. Translated from a reprint from REFA Nachrichten by Purdue Cardiac Project, 1956.
2. MORRIS, W. H. M.: Energy requirements on the farm and in the home. Personal communication, 1956.
3. WUEST, J., GEDDES, D. D. AND ENTERLINE, P.: Energy expenditure of cardiac workers on the job and a comparison with non-cardiac workers. Personal communication, 1956.
4. BRUCE, R. A.: Evaluation of functional capacity and exercise tolerance of cardiac patients. Mod. Concepts Cardiovas. Dis. April, 1956.
5. LEVENSON, R. M.: Exercise tolerance of the cardiac patient. Northwest Med. January, 1956.
6. SPARKMAN, D. R. AND WILSON, J. L.: Evaluation of the cardiac worker. Northwest Med. April, 1956.
7. BRUCE, R. A., LOVEJOY, F. W., JR., YU, P. N. G., MCDOWELL, M. E.: Evaluation and significance of physical fitness for moderate work. Arch. Indust. Hyg. & Occup. Med. **4**: 236, 1951.
8. RUSHMER, R. F.: Cardiac Diagnosis: A physiologic approach. The Cardiac Reserve. Philadelphia, W. B. Saunders Co., 1955, Chapt. 8.
9. FORD, A. B. AND HELLERSTEIN, H. K.: Rehabilitation of the cardiac patient. J.A.M.A. **164**: 225, 1957.
10. PASSMORE, R. AND DURNIN, J. V. G. A.: Human energy expenditure. Physiol. Rev. **35**: 801, 1955.
11. HELLERSTEIN, H. K. AND GOLDSTON, E.: Rehabilitation of patient with heart disease. Postgrad. Med. **15**: 265, 1954.
12. HURLEY, A. M. AND SPARKMAN, D. R.: Psychiatric evaluation of patients undergoing cardiac work evaluation. Circulation **14**: 956, 1956.

CLINICAL PROGRESS

Echinococcus Disease of the Heart

By Jorge Dighiero, M.D., Eduardo Joaquin Canabal, M.D., Cesar V. Aguirre, M.D., Jacobo Hazan, M.D., and José O. Horjales, M.D.

In Uruguay, and in other sheep-grazing countries such as Argentina, Australia, New Zealand, and in the Mediterranean area, echinococcus disease is frequent. Publications relative to cardiac localization of the disease have been few, however.

A careful search of the literature reveals approximately 300 reported cases of echinococcus disease of the heart. We believe, however, that this condition is more frequent than supposed, because cysts located in the territory of distribution of the systemic circulation (spleen, kidneys, brain, muscle), are not uncommon.

Etiology, Pathogenesis, and Incidence

Echinococcus disease in man is caused by the development of the larval stage of the *Taenia echinococcus,* a cestode tapeworm whose definitive host is the dog in most instances. The dog is infested when fed with cyst-bearing organs (lungs, liver, etc.) of intermediate hosts, usually sheep. These cysts, "water vesicles," contain tapeworm heads (scolex) by the thousands, which develop in the intestine of the dog into the adult form of the cestode. The taenia, of rather small size (4 to 5 mm.), has a head, a neck, and 2 body segments or rings. A double line of hooklets and 4 suckers in the head of each worm help it to get anchored to the intestinal mucosa of the host. The last proglottid containing the sexual organs, when distended by the ova, is shed in the feces of the dog, thus contaminating grass and water that may be ingested by the intermediate host, i.e., sheep. Owing to close contact with infested dogs in rural areas, man may become readily contaminated.

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The chitinous shell of the ova of *Taenia echinococcus* is dissolved in the gastrointestinal tract of the intermediate host (man, sheep), thus liberating a hexacanth (6 hooklets) embryo, which then passes through the gastric or intestinal wall to reach the portal circulation and the liver, the organ most frequently involved by echinococcus disease. Occasionally, the liver may be spared because of the rather small size of the hexacanth embryo and the distensibility of hepatic capillaries. If so, the embryo goes on its way down the pulmonary capillary circulation, where it may be blocked. Pulmonary cysts are second to hepatic ones in incidence. This second capillary barrier may also be passed by the parasite, however.

Most classic authors believed that echinococcus disease of the heart was predominantly or exclusively secondary to rupture of a primary hydatid cyst elsewhere in the body and grafting of the hexacanth embryo on the endocardial surface of the right heart chambers, which were more commonly involved than the left.[1] From its original endocardial graft the embryo would be able to reach any other region of the heart by active movements.

Based on a study of over 100 cases and on laboratory experiments, Dévé[2-10] stated that the hydatid cyst of the heart is always primary and single,[11, 12] even in those cases with other than cardiac localizations.[13] According to him and to most modern authors[14-18] the hexacanth embryo, after passing through the capillary networks of the liver and lungs, arrives in the left heart chambers, reaches the coronary circulation and becomes lodged in the interstitial tissue of the myocardium of any 1 of the 4 heart chambers or cardiac septa. Dévé[8] also pointed out that the primary hydatid cyst is more frequently located in the

wall of the left rather than the right heart chambers, particularly the ventricle, because of the richer coronary circulation. Our own experience, based on the observation of 16 cases[19-26] confirms this conclusion (in 11 cases the cysts were located in the left ventricle).

Although Dévé's views on the pathogenesis of echinococcus disease of the heart have had world-wide acceptance, some authors[27] recently proposed the theory that the hexacanth embryo can reach the heart via the lymphatic system (chyliferous→thoracic duct→subclavian vein→right heart chambers→pulmonary capillary network→left heart chambers→coronary network), based on the observation of many cases of cardiac echinococcosis without concomitant hepatic cysts, on the bigger size of the hexacanth embryo as compared with that of the hepatic and pulmonary capillaries and on the finding of ganglionic echinococcosis in some animals (sheep). They also accept the possibility of transendocardial migration of the embryo once it has arrived in the right heart chambers.

Several authors state that cardiac cysts are seen in about 0.5 to 2 per cent of all cases of human hydatidosis.

Analysis of 30 cases of hydatid cardiac cysts in our country[20] shows that the incidence is higher in men than in women (2:1 ratio). Other statistics are in accordance with this proportion.

Most cases occur in the second to fifth decades in patients living in cattle-raising areas.[14, 18, 28]

Pathology

In a few weeks after its arrival in the interstitial tissue of the myocardium of any part of the heart, the hexacanth embryo becomes vesicular, grows slowly but steadily into a unilocular hydatid vesicle with an outer elastic membrane doubled by an inner germinative layer containing a colorless "rock water" fluid called hydatid fluid.

The hydatid vesicle thins out the myocardial wall during its process of growth and exerts pressure on the surrounding muscle fibers, which become more or less ischemic depending on the degree of pressure caused by the parasite and the resistance of the cardiac tissues. Due to mechanical, toxic, allergic, and inflammatory phenomena caused by the hydatic vesicle, the tissue reaction in the host leads to the formation of a fibrous capsule called adventitia (adventitious cyst, according to Dévé[10]) showing cellular infiltration which becomes gradually thicker with time.

The internal germinative layer of the primitive hydatid vesicle, by a process of proliferation, gives rise to multiple vesiculated structures called "brood capsules" (proligerous capsules), which may float in the fluid. From these capsules scolex may develop. If hydatid fluid of a primary unilocular cyst is centrifuged, the so-called "hydatid sand" containing numerous brood capsules and free scolex can be obtained. These 2 elements are of utmost importance in the spread of echinococcus disease in the same individual.

"Due to the particular density of the myocardium, the development of the primary hydatid cyst is restrained. This phenomenon is more obvious when the cyst is located in either ventricle. This is the reason why in most cases there is a reactive daughter cyst formation (multivesicular cyst) and why the primary cyst undergoes other changes such as degeneration or suppuration."[19] Daughter cysts are smaller cysts contained within the primitive or "mother" cyst. They also show an external laminated capsule, an internal germinative layer, hydatid fluid, brood capsules, and scolex.

"When one or more of these changes take place, the adventitia becomes thicker, denser, and even partially calcified and causes comparatively more harm to the surrounding myocardial structures."[19] Other histologic changes like perihydatid granulomata, hydatid pseudotuberculosis, etc.[3] have been described in this condition. In some cases of profound alterations of the primitive hydatid cyst one may find an amorphous substance called "hydatid putty," but none of its normal contents.

According to postmortem and surgical reports, the size of the primitive uncomplicated hydatid cyst of the heart varies from that of a pea to a grapefruit. During the period of

intramural development of the cyst, its presence may be completely overlooked, but later it may produce a localized bulge in the cardiac silhouette that permits roentgenologic recognition of the disease.

The primary hydatid cyst of the heart has a marked tendency to rupture either into the lumen of a cardiac chamber or into the pericardial sac, depending on its primary location and on the direction of least resistance. The primary cyst may also rupture into the myocardium itself (local secondary echinococcosis). While the pericardium usually reacts in front of a hydatid cyst by developing adhesions, the endocardium does not react and is therefore easily invaded by the cyst.

The accident of rupture (single or multiple) of a hydatid cyst of the heart may give rise to different complications.

Uncomplicated Echinococcus Disease of the Heart

According to most authors, "uncomplicated echinococcosis of the heart remains often silent and latent."[8] Our own experience and that of others demonstrates that uncomplicated hydatid disease of the heart has no particular clinical picture. However, in some instances, thoracic pains,[12] palpitation,[29] paroxysmal tachycardia,[30] various murmurs, congestive heart failure,[31] angina pectoris,[32] etc., may occur. But most cases of this disease have been suspected initially by roentgenologic examination.[19, 33, 34]

Roentgenology (fluoroscopy, roentgenograms, tomography, kymography) represents a diagnostic means of highest importance in the detection of the disease, because the deformities of the cardiac silhouette and the calcifications may be easily discovered and studied in all projections.[19] Information regarding the size, shape, and location of the abnormal mass, its contour, its movements, and the characteristics of the calcification may be obtained. Every shadow of calcific density projected in the periphery of the heart should raise the possibility of a hydatid cyst, if signs of constrictive pericarditis are not present. "When spotty areas of calcification are seen in the cardiac shadow, one may also think of echinococcus disease, if calcification of the heart valves can be ruled out. Intramural fibromas may also calcify, but this disease is extremely rare."[19, 35]

Angiocardiography gives valuable information on the deformities caused by the intramural development of a hydatid cyst in the internal outline of the cardiac chambers and on the thickness of the myocardial wall underlying the cyst.[12, 19]

Electrocardiography, according to our own experience,[11, 12, 19-24, 36, 37] is important. Compression ischemia of myocardial fibers and the thinning out of the myocardial wall produced by the cyst cause various electrocardiographic abnormalities. The standard, the unipolar limb, and multiple precordial, back, and esophageal leads must be used in every case of ventricular location of the disease in a search for a pattern of circumscribed ischemia and changes in the QRS complexes. Atrial cysts may or may not cause changes in the P waves. Abnormalities in the P-R interval and QRS complexes (notching, slurring, widening) have been described in cases of septal cysts.[38]

In every case of possible echinococcus disease of the heart various laboratory examinations are indicated. Eosinophilia (7 per cent or more) may be of diagnostic significance, but it is often absent in old, altered cysts. Other conditions also are accompanied by eosinophilia. The intradermal (Casoni) test is only of diagnostic value when positive, particularly, late positive. Several well-established cases of hydatid cardiac disease have repeatedly shown negative intradermal tests.[12, 19] Complement-fixation tests (Weinberg, Ghedini, Imaz-Appathie, and Lorentz) have proved to be not entirely specific.

Complications

The natural history of the primitive myocardial hydatid cyst is interrupted by its rupture in most instances, although occasionally the primitive cyst may remain alive and quiescent for a long time or death of the para-

site may occur, with subsequent spontaneous cure of the disease.

Rupture of the primitive myocardial cyst into the endocardial cavity, the pericardial sac, or the myocardium itself may produce a series of complications, depending on the way it happens (small fissure in the hydatid membrane and the adventitious cyst, wide open rupture, recurrent ruptures) and on its contents (unilocular cyst, multivesicular cyst, cyst with different alterations). If the opening in a subendocardial fertile hydatid cyst is small (fissure), only hydatid fluid containing free scolex and brood capsules escapes. This accident usually provokes a rapid onset of hyperergic phenomena of varying intensity, i.e., anaphylactic shock, urticaria, fever, and diarrhea. Late complications may occur owing to the evolution of hydatid material (scolex) distant from the primitive cyst (metastatic echinococcosis of the lesser or systemic circulation). If this accident supervenes in a subepicardial cyst, an acute or subacute serofibrinous or purulent pericarditis with a high percentage of eosinophils may ensue. Secondary echinococcosis of the pericardium represents a late complication.[9, 22]

When the primitive myocardial cyst freely ruptures into the cardiac cavity, two different kinds of complications may appear. Immediate ones are represented by the hyperergic phenomena mentioned above, which may be fatal, may allow the patient's survival, or may even be overlooked in some cases. Late complications, besides metastatic echinococcosis of the lesser or systemic circulation[17, 18, 20] due to "the liberation, the dissemination and the distant colonization of living parasitic elements (scolex) proceeding from the primitive lesion,"[9] are caused by the embolization of fragments or of the entire membrane of the primitive hydatid cyst, of daughter cysts (living or dead) and of hydatid debris to the lesser or systemic circulation.[23, 26, 28, 40-42] These serious complications are not always late. Some cases of sudden death immediately after rupture of the hydatid cyst into the cardiac cavities are due to intracardiac blockade or pulmonary or cerebral embolism by daughter cysts or fragments of hydatid membrane.[8, 28, 43] Similar complications are seen in cases of hydatid cysts of the liver rupturing into the inferior vena cava.[25, 44, 45]

Depending on the contents of the primitive cyst rupturing into the pericardial sac, different forms of chronic pericarditis are encountered. Hydatidopericardium is a chronic generalized or localized (due to adhesions) pericarditis with hydatid material in evolution (living daughter cysts) or involution (fragments of membrane pertaining to the "mother" cyst or dead daughter cysts or both). A purulent pericardial effusion, in addition to hydatid material, is usually present,[48, 49] although cases with no effusion have been described (? reabsorption).[38] Hydatidopericardium may remain quiescent for a long time, may give symptoms and signs of cardiac compression,[50] or be even invasive (pseudoaneurysmatic form).[47, 51, 52] These events are due to the fact that living daughter cysts containing fertile elements (scolex) may continue to grow outside the mother cyst. This phenomenon also takes place in cases of embolization of daughter cysts to the lesser[23, 40] or systemic[6, 7] circulation causing, besides subtotal or total arterial obstruction, hydatid arterial aneurysms and a secondary intraarterial echinococcosis. As any living daughter cyst may rupture wherever it be located, further complications of the disease can be expected.[23, 29, 51]

Practically all forms of hydatid pericarditis cause thickening of the pericardium. Constrictive pericarditis has been described in cases of protracted evolution of an overlooked hydatidopericardium.[50] Secondary echinococcosis of the pericardium is frequently associated with hydatidopericardium.[48] Secondary cysts (pericardial grafts), as well as daughter cysts proceeding from the primitive myocardial hydatid cyst, may eventually rupture into the cardiac chambers.[41, 53]

It is to be emphasized that *diagnosis of hydatid disease of the heart must be made in the early, uncomplicated stages of the disease prior to the occurrence of any one of its common and dreaded complications.* Other-

wise, little or nothing can be done for the benefit of the patients in most cases.

Summary

The etiology, pathogenesis, pathology, and the clinical picture of uncomplicated and complicated echinococcus disease of the heart are discussed.

Cardiac location of the larval stage of *Taenia echinococcus* in human beings is not an uncommon disease in sheep-grazing countries. The authors put special emphasis on the methods helping to establish the diagnosis of the condition prior to the appearance of any one of its dreaded complications, which make treatment much more difficult and prognosis considerably poorer.

Summario in Interlingua

Es discutite le etiologia, pathogenese, pathologia, e tableau clinic de noncomplicate e complicate morbo cardiac e echinococcos.

Le location cardiac de *Taenia echinococcus* in le stadio larval non es un phenomeno incommun in humanos in paises a cultura de oves. Le autores sublinea specialmente le methodos que es de adjuta in establir le diagnose del condition ante le manifestation de ulle de su timibile complicationes que rende le tractamento multo plus difficile e le prognose considerabilemente minus favorabile.

REFERENCES

1. Peters, J. H., Dexter, L. and Weiss, S.: Clinical and theoretical considerations of involvement of the left side of the heart with echinococcal cysts. Am. Heart J. **29**: 143, 1945.
2. Dévé, F.: De l'échinococcose sécondaire. Thèse de Paris, 1901.
3. —: De l'échinococcose sécondaire embolique. Compt. rend. Soc. de biol. **53**: 608, 1901.
4. —: La rupture itérative des kystes hydatiques du coeur. Compt. rend. Soc. de biol. **79**: 415, 1916.
5. —: Echinococcose cérebrale métastatique. Compt. rend. Soc. de biol. **81**: 633, 1918.
6. —: L'anévrysme hydatique. Compt. rend. Soc. de biol. **90**: 552, 1927.
7. —: Embolies hydatiques pulmonaires à siège périartériel (geodes périartérielles emboliques). Compt. rend. Soc. de biol. **90**: 554, 1927.
8. —: Les kystes hydatiques du coeur et leurs complications. Abstracted, Algérie Méd. May, 1928.
9. —: L'échinococcose secondaire. Paris, Masson et Cie, 1946.
10. —: L'échinococcose primitive. Paris, Masson et Cie, 1949.
11. Armand-Ugon, V., Piaggio, Blanco, R. A., Mezzera, J. R., Aguirre, C. V. and Purcallas, J.: Quiste hidático del ventrículo izquierdo operado. Rev. tuberc. Uruguay. **19**: 57, 1951.
12. Bosch del Marco, L. M., Canabal, E. J., Dighiero, J., Baldomir, J. M., Suzacq, C. V., and Antiga, P. F.: Quiste hidático del corazón localizado en el ventrículo izquierdo. Operación. Curación. Arch. urug. de med., cir. y especialid. **41**: 159, 1952.
13. Pérez Fontana, V. and Sapriza, J. P.: Quiste hidático hialino del ventrículo izquierdo. Arch. Intern. Hidatid. **13**: 157, 1953.
14. Dew, H. R.: Hydatid Disease. Sydney, The Australasian Medical Publishing Co., 1928.
15. Bourgeon, R.: Les kystes hydatiques du coeur. Thèse d'Alger, 1940.
16. Piaggio Blanco, R. A. and García Capurro, F.: Equinococosis Pulmonar. Bueonos Aires, Editorial "El Ateneo," 1939.
17. Boppe-Dévé, M.: L'échinococcose pulmonaire métastatique. Thèse de Paris, 1916.
18. Dumont, M.: L'échinococcose cérebrale métastatique. Thèse de Toulouse, 1918.
19. Canabal, E. J., Dighiero, J., Aguirre, C. V., Purcallas, J., Baldomir, J. M. and Suzacq, C. V.: Echinococcus disease of the left ventricle: A clinical, radiologic and electrocardiographic study. Circulation **12**: 520, 1955.
20. —, —, —, Baldomir, J. M., Purcallas, J., Suzacq, C. V., Horjales, J. O., Scremini Algorta, P. and Hazan, J.: Equinococosis cardíaca. Arch. Intern. Hidatid. **15**: In press.
21. Canabal, E. J.: Quiste hidático cerrado del ventrículo izquierdo. Su estudio angiocardiográfico y electrocardiográfico. Trabajo de Adscripción, Thesis. Facultad de Medicina. Montevideo, 1951.
22. Piaggio Blanco, R. A., Roglia, J. L., Pertusso, J. C., Dighiero, J. and Canabal, E. J.: Quiste hidático del ventrículo izquierdo roto en el pericardio. Pericarditis hidática. Tratamiento quirúrgico. Arch. urug. de med. cir. y especialid. **38**: 1, 1951.
23. —, Dubourdieu, J., Dighiero, J., Canabal, E. J. and Grosso, O. F.: Quiste hidático de la aurícula derecha, equinococosis pulmonar metastática y corazón pulmonar crónico hidático causado por una obstrucción parasitaria de la arteria pulmonar izquierda y de sus ramas. Arch. urug. de med. cir. y especialid. **36**: 530, 1950.

24. Canabal, E. J., Dighiero, J., Aguirre, C. V., Baldomir, J. M., Purcallas, J., Suzacq, C. V., Horjales, J. O., Hazan, J. and Scremini Algorta, P.: Nuestra experiencia en el tema de la equinococosis cardíaca. An. Fac. Med. Montevideo **15**: In press.
25. Aguirre, C. V., Purcallas, J., Baldomir, J. M., Suzacq, C. V., Hazan, J., Horjales, J. O., Dighiero, J. and Canabal, E. J.: Corazón pulmonar agudo hidático. Arch. Inst. cardiol. México **26**: 211, 1956.
26. Dighiero, J., Hazan, J., Horjales, J. O., Suzacq, C. V., Baldomir, J. M., Canabal, E. J., Purcallas, J. and Aguirre, C. V.: Corazón pulmonar crónico hidático. Arch. Inst. cardiol. México. In press.
27. Jorge, J. M. and Re, M.: Hidatidosis cardíaca. Vias de infestación. Arch. Intern. Hidatid. **6**: 87, 1946.
28. Morquio, L.: Kyste hydatique primitif du myocarde ouvert dans le ventricule gauche: hydatose métastatique avec neuf kystes dans le cerveau et deux dystes dans la rate. Arch. méd. enf. **37**: 90, 1934.
29. Litwak, R. S.: Echinococcus disease of the heart. *In* Bailey, C. P. Surgery of the Heart. Philadelphia, Lea and Febiger, 1955, p. 881.
30. Ferrari, M.: Equinococosis cardíaca. *In* Temas de Oncología y de Radioterapia. Montevideo, García Morales-Mercant Gráficos Unidos S.A., 1953, p. 217.
31. Carrau, A. and Moreau, J. E.: Sobre hidatidosis cardíaca. Arch. pediat. Uruguay **1**: 462, 1930.
32. Di Bello, R.: Pericarditis hidática aguda. Clínica **2**: 68, 1953.
33. D'Abreu, A. L.: The removal of a hydatid cyst from the wall of the left ventricle. Thorax **5**: 362, 1950.
34. Attwood, C. J., Sargent, W. H. and Fletcher, T.: Echinococcus cyst of the heart: report of a case. Ann. Int. Med. **15**: 1109, 1941.
35. Mahaim, I.: Les tumeurs et les polypes du coeur. Paris, Masson et Cie, 1945.
36. Piaggio Blanco, R. A., Dighiero, J., Canabal, E. J., Baldomir, J. M., Aguirre, C. V., Purcallas, J. and Suzacq, C. V.: Equinococosis del ventrículo izquierdo. Su perfil electrocardiográfico. An. Fac. med. Montevideo **37**: 310, 1952.
37. Baldomir, J. M., Canabal, E. J., Dighiero, J., Purcallas, J., Aguirre, C. V. and Suzacq, C. V.: Valor del electrocardiograma para establecer el diagnóstico diferencial entre los aneurismas y los quistes hidáticos del ventrículo izquierdo. Arch. urug. de med. cir. y especialid **42**: 273, 1953.
38. Agote, L., Goyena, J. R. and Bianchi, A. E.: Hidatidosis del corazón. Semana méd. **39**: 1717, 1927.
39. Piaggio Blanco, R. A.: Equinococosis pulmonar múltiple. An. Fac. med. Montevideo **23**: 135, 1938.
40. Amargós, A., Menéndez, H., and Di Bello, R.: Cor pulmonale hidatidíco. Día méd. **20**: 600, 1948.
41. Brito Foresti, C. and Bonaba, J.: Un cas de kystes hydatiques viscéraux (coeur, cerveau, reins). Rupture de l'un des kystes du coeur dans l' oreillette gauche. Constatation a l' autopsie de vesicules filles libres a l' intérieur des cavités cardiaques gauches. Integrité du foie et de poumons. Bull. et mém. Soc. méd. Hôp. de Paris. **38**: 262, 1914.
42. Pérez Fontana, V., Rodríguez, B., and Rodríguez Barrios, R.: Quistes hidáticos del cerebro. Arch. Intern. Hidatid. **4**: 263, 1938.
43. Heimann, H. L.: Hydatid cyst in the heart. Brit. M. J. **1**: 801, 1928.
44. Castiglioni Alonso, H.: Quiste hidático del higado abierto en la vena cava inferior. Arch. Intern. Hidatid **1**: 269, 1935.
45. Urioste, J. P., Piaggio Blanco, R. A. and Artagaveytia, A. C.: Dos casos de quiste hidático de higado abiertos en la vena cava inferior. Arch. urug. de med. cir. y especialid **8**: 226, 1936.
46. Masovcic, U.: Ueber einen Fall von Echinococcus Hydatidosus des Herzmuskels. Wien. med. Wchnschr. **54**: 451, 1904.
47. Amargós, A., Armand-Ugon, V., Larghero, P. and Di Bello, R.: Tres casos de equinococosis cardiopericárdica operados. Arch. urug. de med. cir. y especialid **30**: 483, 1947.
48. Vigil, E., Pineyrúa, J., and Diez, R.: Hidatidosis cardiopericárdia. Arch. urug. de med. cir. y. especialid. **30**: 483, 1947.
49. Dungal, N.: Echinokokkus des Herzens. Acta path. et microbiol. scandinav. **15**: 90, 1938.
50. Larghero, P., Di Bello, R. and Victorica, A.: Pericarditis constrictiva hidática. Bol. Soc. de cir. de Rosario **21**: 17, 1950.
51. Larghero, P.: Tratamiento del quiste hidático del ventrículo izquierdo. Diez observaciones en el Uruguay. El Tórax **3**: 263, 1954.
52. Hatzieganu, I., Vasiliu, T. and Moga, C.: Le kyste hydatique du coeur simulant un anévrysme. Arch. mal. coeur **29**: 72, 1936.
53. Dévé, F. and Jirou, M.: Kyste hydatique du coeur compliqué d' échinococcose séeondaire du pericarde. Mort subite par rupture d' un des kystes périeardiques dans l' oreillette gauche. Presse méd. **28**: 1081, 1920.

BOOK REVIEWS

New Bases of Electrocardiography. *Demetrio Sodi-Pollares,* with the collaboration of *Royall M. Calder,* Editor, English translation. St. Louis, C. V. Mosby Company, 1956, 772 pages, 523 figures. $18.50.

In reviewing this book on electrocardiography a quotation from the foreword written by Dr. Ignacio Chavez of the Institute of Cardiology in Mexico City, Mexico, is very pertinent.

"The clinician has available for learning diagnostic electrocardiography, many books, large and small, some in the form of atlases, others as manuals or treatises; but books that teach and discuss the scientific bases on which the procedure rests, or all the experimental work that has been done to elaborate it, are very few. Such a book is what Dr. Sodi-Pallares gives us here . . . . It is not a treatise on clinical electrocardiography but a book concerned with the 'hows' and the 'wherefores' in electrocardiography. It is not intended for the presentation of established formulas, but to present methods for the better understanding of the tracings and to interpret them in the light of what we now know concerning the electrophysiology of the heart."

In the opinion of the reviewer, the authors have accomplished these aims in a superlative fashion. If more physicians were familiar with the basic material presented in this volume and used the approach, demanded by the authors, in their daily reading of electrocardiograms, the quality of electrocardiographic interpretation would be enormously improved.

The first 4 chapters in the book are concerned with principles of electricity, the electrophysiology of the heart, and matters relating to the electric axis of the heart and the limb leads. Chapter V is devoted entirely to the electric effects due to injury of cardiac muscle and in Chapter VI the reader will find detailed discussion of the behavior of precordial leads and the reasons why certain changes occur in hypertrophy, bundle-branch block, myocardial infarction, and in other conditions. Chapter VII is concerned with the activation process in the human heart and, in this section, much experimental as well as clinical evidence, pertaining to the pathways of excitation in normal intraventricular conduction and in bundle-branch block, is presented. The electric and anatomic positions of the heart are discussed in Chapter VIII, and Chapter IX is devoted to vectorcardiography and stereovectorcardiography. Chapters X and XI are concerned with the ventricular gradient and potentials within the cavities of the ventricles, respectively, and in the Appendix many derivations and explanations, mostly mathematical in character, which expand and clarify matters referred to elsewhere in the book, will be found.

Although the book is, in part, a translation of the third edition of *Nuevas Bases de la Electrocardiographia* by Sodi-Pollares, it does not suffer from the deficiencies that occasionally occur under such circumstances. The text is clear and well written and the illustrations are adequate in number and of excellent quality. It is difficult to find any feature of this volume that justifies unfavorable criticism. If the title were changed to something like "Basic Principles of Electrocardiography (or Electrocardiographic Interpretation)" it might be more informative of the character of this book than is the title employed. Irrespective of its title, this book should be in the library of every physician seriously interested in electrocardiography.

FRANKLIN D. JOHNSTON

Venous Return. *Gerhard A. Brecher.* New York Grune and Stratton, Inc., 1956, 141 pages, 55 figures. $6.75.

This small monograph, dealing specifically with the dynamics of venous return, may prove to be the most significant single contribution to basic hemodynamics since C. J. Wiggers' *Pressure Pulses in the Cardiovascular System* (1928). It is appropriate that Dr. Wiggers provided the foreword in this volume.

Dr. Brecher and colleagues have vigorously attacked and seemingly solved the 2 most vexing problems concerned with the dynamics of venous return. Moreover, he has provided us with a lucid and readable account of why and how they did it.

The 2 basic questions asked and answered in this monograph are: (a) does inspiration increase venous return to the heart; and, (b), does the heart pull blood from the veins (*vis a fronte*) as well as push it through the venous system (*vis a tergo*). The answer turns out to be "Yes" in both cases, but learning the answers from the monograph is a completely enjoyable experience, complete with a careful and thorough historical survey and convincing experimental documentation.

The first 3 chapters are devoted to establishing the historical background, reviewing elementary hemodynamic principles, and the peculiarities of the venous system. The fourth chapter sum-

marizes the areas of controversy, particularly dealing with the "venous collapse" theory of Holt and Duomarco as related to the effect of respiration and with the controversy as to whether the ventricles can "suck" blood into their cavities during either systole or diastole. This chapter also provides a place to point out that much of the controversy existed because of inadequate methods of measuring venous blood flow. Chapter V follows with an excellent critique of flowmeters and their application. The description of the bristle flowmeter developed in the author's laboratory will be of interest to many readers.

The presentation of experimental material begins in Chapter VI and continues through Chapter IX. It progresses methodically and surely through an elucidation of venous hemodynamics, the effect of respiration on venous return (including artificial respiration), and the heart's action on the venous return. Positive evidence is provided that inspiration (and alternating positive-negative artificial respiration) increases venous return. A highly satisfactory compromise between the intrathoracic aspiration theory and the "venous collapse" theory is achieved. Both are correct. The evidence for a *vis a fronte* during ventricular systole is good, thus necessitating the adoption of a concept of the heart as a reciprocating pump (push-pull) rather than a pressure pump only.

The last 2 chapters try to apply the new knowledge of venous hemodynamics to problems concerned with atrioventricular valvular disease and intracardiac surgery. Although not greatly detailed, these 2 chapters do summarize present problems and technics in these areas and indicate the direction for further progress.

The reproductions of the original records are unusually large and show detail very well. The technical excellence of the tracings is worthy of notice. The diagrams are large and understandable.

DAVID F. OPDYKE

La Balistocardiographie (Valeur Pratique). *J. Desruelles* and *J. F. Merlen.* Paris, Expansion Scientifique Francaise, 1957, 208 pages, 108 figures. 2,200 francs.

The authors state that their purpose in the preparation of this book was to introduce ballistocardiography to those unfamiliar with it. This objective they have accomplished. An early chapter presents in an elementary way the physical basis of ballistocardiography. There follows a discussion of several simple recording methods, conventional descriptions of "normal" and "abnormal" records, and finally a presentation of the kinds of abnormal records found in various disorders of the circulatory system.

The book contains nothing significantly new but it is useful as a good review of a controversial subject. There is only brief mention of newer approaches to ballistocardiography such as ultra-low frequency recording and basic physiologic study under controlled experimental conditions. In a final brief chapter upon the clinical value of ballistocardiography the authors take a wisely conservative position. With particular reference to coronary artery disease they point out that there is hope that further experience with ballistocardiography will prove that it provides the clinician with useful information not provided by other methods of study.

BENJAMIN M. BAKER

Clinical Physiology. The functional pathology of disease. *Arthur Grollman,* Editor. New York, McGraw-Hill Book Co., Inc., 1957, 854 pages. $12.50.

As indicated in the preface, this book aims to present the basic physiologic principles of clinical medicine to senior medical students, interns, and practitioners. The term physiology is used in a broad sense to include biochemistry and pathology, and to a lesser extent, anatomy, pharmacology, and bacteriology. Subject matter is divided into 9 principal parts: general metabolic considerations, the cardiovascular, respiratory, digestive, hematopoietic, endocrine, renal excretory, and locomotor systems, and infection and immunity. Emphasis is placed on metabolic, cardiovascular, and endocrine fields where more significant advances have occurred in recent years.

The book succeeds in its stated aim, with minor qualifications. Despite competent editorial effort, there is unevenness in the 33 chapters written by a total of 23 senior authors. Thus some portions of the chapters on water and electrolyte metabolism, electrocardiography, congenital heart disease, and coagulation will be difficult for the average reader to comprehend. On the other hand, the chapters on vitamins, congestive heart failure, adenohypophysis, and male and female sex organs are exceptionally lucid. The remaining chapters are well presented. In view of the frequency of neuroses and neurologic disturbances in medical practice, more considerations of the central nervous system is desirable.

Inaccuracies are few. Thus, the normal diurnal variation in body temperature is stated to be 3 F. (p. 10) and reference to accessory vasomotor-respiratory centers in the carotid and aortic bodies (p. 406) is unusual terminology. Typographic errors are minimal, particularly for a first edition.

The book is definitely recommended to junior and senior medical students, interns, residents, and generalist and specialist practitioners.

GEORGE E. WAKERLIN

Les Angors Coronariens Intriques. Étude clinique et expérimentale des inter-réactions neuro et viscéro-coronariennes. *Roger Froment* and *André Gonin.* Paris, Expansion Scientifique Francaise, 1956, 173 pages, 33 figures.

These well known French clinicians have here attempted a very difficult task, namely a detailed consideration of certain unusual coronary pain patterns, whose location, radiation, duration, provocation, or response to nitroglycerin, is atypical due to the influence of co-existing but noncardiac disease or dysfunction. These anomalous clinical pictures, they believe, are effected by the interweaving of neurovisceral reflexes with the reactions of the coronary circulation and do not result from the simple but independent co-existence of 2 maladies. The authors recognize that these complex cases of combined coronary and somatic pains have been of interest to many others and cite them liberally.

The book is divided into 3 sections: the first represents the authors' own clinical experience with 30 patients over a 12-year period, the second a short report of the authors' animal experiments on the subject, and finally the third section offers a discussion of the pathogenesis of this interdependence of coronary and extracoronary disorders. In the first section, the various types of pain patterns are carefully detailed and are divided into several groups. The first describes coronary pain in patients with a highly emotional constitution in whom one finds not only neurotic or psychoneurotic overtones but also imbalance of the vegetative nervous system; these may exhibit weird irradiations of pain (e.g., to the left toes) or pains may be accompanied by singultus, flushing of the skin, gaseous eructations, deep sighs, and other emotional expressions of anxiety. A second and the largest group consists of patients with coronary pain interwoven with, even provoked by, vertebral disease. The interchange of influence of the 2 diseases in these cases can be so constant, in the authors' experience, that a continual state of pain may eventuate, thus complicating the etiologic diagnosis as regards the coronary component. A third clinical group is composed of patients with combined coronary and digestive tract disorders—primarily peptic ulcer, hiatus hernia, and gallbladder or esophageal diseases. In the fourth group the authors imply that pulmonary disease and its sequelae, especially chronic paroxysms of cough, evoke anginal pain. Although the authors are of the opinion that certain complex nervous or visceral reflexes influence the already abnormal coronaries it appears more likely to the reviewer that the actual effort of coughing, and the anoxic state of the emphysematous subject, are the responsible physiologic mechanisms that act directly to hamper myocardial nourishment. In the final but heterogeneous group there are several interesting descriptions of subjects with amputation stumps and phantom anginal arm pain.

The authors state that a careful historical interrogation is the most important approach in unraveling these intricate pain patterns. A change in the usual behavior of the anginal discomfort should of course prompt consideration of an acceleration of the vascular disease, as the authors remind us, but once this is eliminated as cause, a separate disease entity, which has interwoven itself into the pain picture should be considered. If the case presents first in its fully developed complexity it is usual to find electrocardiographic evidence suggestive of heart disease in the authors' experience. The history often reveals that typical anginal pain predated the complex and bizarre status and with the change in symptoms one should conclude that a new disease picture is making itself felt. Treatment of the associated disease will often relieve the patient of certain of the painful symptoms and clarify the picture.

The experimental design in the second section of the book is unfortunately so simplified that conclusions should be made with reserve. The authors utilize only directional T-wave changes in the dog as evidence of coronary vasomotricity. In these studies, the latter is solicited by 1 of 4 maneuvers —excitation of the first 3 cervical nerves, and distention of esophagus, stomach, or gallbladder respectively. These stimuli are applied in dogs with intact as well as dogs with compromised coronary vessels. T waves were altered in some dogs of every group, but more often in those with altered coronary circulation.

The third section of the book presents with great skill a discussion of the possible pathogenesis of these complex and interwoven painful symptoms the origins of which, it would seem, at times are at somatic areas very remote from the diseased organs. Sensitization of certain spinal segments with facilitation and augmentation and even dissemination of the stimuli outside usual pathways is held by the authors, and supported by numerous references to the neurophysiologic literature, to be responsible for the summation or distortion of certain painful symptoms or their peculiar irradiation or duration.

This is a valuable presentation of a very difficult clinical problem. One might at first feel the clinical descriptions that make up the first section are overlong, but the atypical anginal pain patterns must be clearly defined to be understood. One might be concerned that the authors accept T-wave changes, in both the clinical records and the experimental protocols, as incontrovertible evidence of coronary disease, especially since the tracings shown are not always convincing and occasionally technically too poorly reproduced for the reader

to interpret. (In figure 13 leads V_L and V_F are mounted upside down and hence interpretation of V_L is incorrect.) The English summaries at the ends of chapters are unfortunately so poor (in terms of language) that they will be of little value. Everyone interested in the intricacies and difficulties encountered in, as well as the treatment of, these complex coronary subjects will benefit by studying the findings presented in this volume. The beautifully detailed clinical descriptions and the provocative discussion of mechanisms warrant a full English translation.

M. IRENÉ FERRER

Coronary Heart Disease. Angina pectoris; myocardial infarction. *Milton Plotz.* New York, Paul B. Hoeber, Inc., 1957, 353 pages, 107 figures. $12.00.

Because of the increasingly narrow specialization within the field of internal medicine, it is not surprising that a book such as this should seem desirable, and even essential. The consideration of coronary heart disease is far more extensive and detailed than that in any other book known to this reviewer. To one who has not seen it the number of pages might seem excessive; to one who has read it carefully and critically from cover to cover there does not appear to be one word too many.

One would expect any such book to contain chapters dealing with etiology, pathology, diagnosis, prognosis, and treatment. This one has in addition chapters devoted to anticoagulant therapy, surgical treatment, the possibilities of prevention, diet, and medicolegal features of coronary disease. There is an excellent chapter on electrocardiography, followed by nearly 50 pages of case reports, each illustrated by means of full-sized electrocardiograms, beautifully reproduced. Ballistocardiography, lipid metabolism, and the possible effects of tobacco smoking are considered fully in the light of the latest available evidence. Indeed, it would be difficult to think of any aspect of the subject that has not received adequate and expert attention. Each chapter has an extensive bibliography, the number of references ranging from 60 to 270.

It is not the wide coverage and extensive bibliography that alone make this volume such an important one for education and reference. Of far greater importance are the author's familiarity with the clinical and experimental work in this field, his broad clinical knowledge, his admirable judgment, and impressive wisdom. There are few, if any, topics that are not illuminated by his perceptive comments. The brief statements of his own beliefs and practices, which conclude almost every discussion, bear eloquent testimony to his experience, understanding, and balanced judgment. There may possibly be a number of cardiologists who could assemble the enormous amount of material upon which this book is based, but I think there are very few whose experience and training, whose qualities of mind and character, would enable them infallibly to separate the essential from the unessential and to interpret the important facts convincingly, wisely, and modestly. On almost every page the book reveals knowledge derived from the day-by-day care of patients; it could never have been written by one whose life has been spent in teaching and investigation.

In the judgment of this reviewer it is a superb and exciting book, a splendid summation of our knowledge of the disease which, in many parts of the world, is recognized as the most serious and most challenging of all. If cardiologists and internists would use it for constant reference, the diagnosis and treatment of angina and myocardial infarction would improve enormously. To all physicians who accept the responsibility for such diagnosis and treatment, and to all who teach doctors and medical students, it is commended without reservation and with great enthusiasm.

H. M. MARVIN

Pediatric Cardiology. *Alexander S. Nadas.* Philadelphia, W. B. Saunders Company, 1957, 587 pages, 343 figures. $12.00.

There has been an increasing need for a book on cardiology covering diagnosis and treatment of heart conditions encountered in the pediatric age group. The field of congenital heart disease has developed tremendously in the past few decades due both to extraordinary advances in surgery and to clarification of physiopathology and diagnostic findings by cardiac catheterization and angiocardiography. Advances in rheumatic fever with use of prophylaxis and hormone therapy have been striking. The great majority of initial attacks of rheumatic fever occurring in childhood and the very nature of congenital heart disease place these two major etiologic categories of heart disease initially in the hands of pediatricians or general practitioners caring for infants and children.

Several factors are important in the achievement and delineation of optimum total management of cardiac problems as seen in infants and children. A working knowledge is basic concerning children's normal development, their needs, outlets, and activities, both physical and emotional. In the more recently developed field of congenital heart disease extensive clinical experience, as well as personal familiarity both with the special technics of investigation and the related fields in therapy, has been essential to bring the growing information into clear focus for diagnosis, specific treatment, and general management of the individual case. Dr. Nadas has eminent qualifications for writing on pediatric cardiology. With a background as a

well-trained pediatrician he had the benefit of a general pediatric practice in a small community before starting his work as cardiologist in the Children's Medical Center in Boston. The experience of the past 10 years' work in that institution forms the basis for much of the data presented in his book. It is obvious that a close relationship with mutual benefit has existed between the staffs of pediatric cardiology with its physiologic laboratory and the staffs of such allied fields as radiology, surgery, and anesthesia.

The book, which is introduced by Dr. Nadas as a handbook for pediatrician, general practitioner, and medical student, fulfills this purpose admirably as well as being of great value to specialists and teachers in the field. The approach is well rounded and practical.

In the first section dealing with tools of diagnosis, there are many helpful suggestions concerning the standard methods of cardiac examination as applied to children. Chapters on radiology and electrocardiography underscore and illustrate the vital importance in accurate diagnosis of full and integrated use of these technics, especially in congenital heart disease. Cardiac catheterization and angiocardiography both in the descriptive chapters and throughout the book receive appropriate consideration of their value, an equally appropriate respect for risks with consequent well-balanced recommendations as to indication for diagnostic use of these special technics. Excellent clinical description of acute rheumatic fever, its course, and rheumatic heart disease as seen in childhood are drawn from the extensive experience of the House of the Good Samaritan. Indications given for the use of hormone therapy appear sound at current writing. The extreme degrees of restrictions recommended for the entire period when any evidences of active carditis are present can be seriously questioned primarily as to medical justification as well as to psychologic advisability and actual feasibility under most circumstances. Concerning indefinite prophylaxis in rheumatic subjects and mandatory extensive antibiotic therapy for sore throats at large the author is far less stringent in his recommendations.

Other chapters on acquired heart disease dealing with pericarditis, arrythmias, and congestive failure in pediatric practice are excellent. The presentations on hypertension and on myocardial diseases are outstanding. An earlier analysis of conditions grouped as primary myocardial diseases has been amplified, and the author's unusually wide experience in diagnosis and treatment of these rather rare but important differential problems seen particularly in infancy is most valuable.

Over half the book is devoted to congenital heart disease. The incidence and anatomy of each anomaly are briefly described, and physiopathology is clearly outlined, especially as related to the total clinical findings. The importance of variation in effect dependent on the severity of the lesion present in individual cases is well stressed in relation to diagnostic findings, need for special studies, and recommended therapy. Differential diagnosis is particularly well handled. Established methods of surgery in appropriate types of lesions are well described, the risks in each being fairly outlined. The book is of necessity somewhat restricted in respect to surgery as at the time of writing the open-heart technics were only in their earlier stages of development.

A brief, helpful chapter on anesthesia for children with heart disease is included, prepared by Dr. Robert M. Smith, Chief anesthesiologist of the Children's Medical Center.

The style of the book is straightforward, lightened by occasional touches of appropriate humor, and makes for easy reading. The format of the printed page is excellent. Although of considerable length the book is light and readily handled. Illustrations are profuse. Clear diagrams and frequent tabulations of data for differential diagnosis are most effective in summarizing physiologic and clinical data. It is unfortunate that the reproductions have frequently lost clarity of finer details in electrocardiograms and especially of the pulmonary vascular markings in x-rays. References are well selected.

Dr. Nadas has undertaken a large task, fulfilled it with distinction to himself and with great benefit to those who undertake the care of cardiac children, be they pediatricians, general practitioners, or adult cardiologists who quite frequently must advise concerning younger cardiac cases.

JANET S. BALDWIN

The Shoulder and Environs. *James E. Bateman.* St. Louis, The C. V. Mosby Company, 1955, 565 pages, 374 figures. $16.25.

The region of the shoulder girdle presents a most complex area from the viewpoint of the relationship between the numerous structures that pass between the thorax and the head or the thorax and the upper extremities. These are in such close proximity to bony and muscular structures that relatively minor abnormalities in relationships are capable of producing serious secondary complications. Although interest in this field was activated during the past war and has been continued since, the time is long overdue for an authoritative monograph dealing with this subject. Dr. James E. Bateman has produced such a monograph, which should be of the greatest use to internists and specialists in cardiovascular disease as well as to general practitioners and to orthopedic and general surgeons.

The subject matter is carefully developed beginning with the evolution and applied embryology of the shoulder region and with the development of congenital abnormalities. The applied, variational, and radiographic anatomy of the shoulder girdle is dealt with extensively with excellent reproductions. The physiology of the shoulder with the mechanics for all types of motion is covered in detail. Thus a basic pattern for a sound understanding is laid.

The author then develops the technic for examination of the shoulder region and the differential diagnosis of disorders of the shoulder region, including those with shoulder-neck pain as well as those in which shoulder pain and radiating pain predominate. He includes all known possibilities; of particular interest to cardiologists are his sections dealing with cervical rib, the scalenus anticus syndrome, the costoclavicular syndrome, the hyperabduction syndrome, sleep dysesthesias, and many other related conditions. The last chapters deal with nerve injuries, tumors of the shoulder region, fractures and dislocations of the shoulder region, and the assessment of disability in the shoulder region. Since many of these conditions may impinge upon and be associated with vascular problems, the points that are contained in these chapters are also of practical and scientific interest to men who treat diseases of the circulation.

This book is highly recommended for all who have occasion to treat or exhibit an interest in this field.

IRVING S. WRIGHT

Diagnosis and Treatment of Vascular Disorders (Angiology). *Saul S. Samuels, Editor.* Baltimore, The Williams and Wilkins Company, 1956, 621 pages, 232 figures. $16.00.

This book covers all the important aspects of diagnosis and treatment in the field of peripheral vascular diseases. It is edited by Dr. Saul S. Samuels and he has written 3 of the 24 chapters. There are 16 additional contributors to the volume.

Although the book is presented in textbook format it is not well integrated and is more like a series of short monographs presented in chapter form than like a textbook. Many of the chapters are excellent but several show a lack of detailed knowledge of historical and clinical aspects of the subject.

Unfortunately no consistent classification or terminology (such as that of the American Heart Association) is followed throughout the book. In some parts of the book the inconsistent terminology is confusing, as is the use of nonspecific terms such as "vessel" instead of "artery" when exclusively arterial disease is discussed.

The chapter title "Arteriosclerosis — Atherosclerosis in Relation to Diabetes" is misleading, as the chapter is largely concerned with the general problem of arteriosclerosis and atherosclerosis, and the association with diabetes is considered only incidentally.

Opinions expressed in some of the chapters, especially those entitled "Senile Obliterative Arteritis" and "Endarteritis Obliterans," are controversial and as presented by the author of the chapter are not supported sufficiently by detailed factual evidence to be included in a textbook that may be used by many physicians not as yet experienced in the field of peripheral vascular diseases. Also, in the chapter entitled "Senile Obliterative Arteritis," too much dependence is placed on aortography and arteriography rather than on histologic examination for interpretation of underlying pathology.

With so many contributing authors some conflicts of opinion and overlapping of discussions are unavoidable. However, there are several important places in this book where there are contradictions, or at least serious differences of opinion, which would confound the reader inexperienced in vascular diseases and would frustrate the experienced reader. In several chapters the histamine flare test is stated to be of considerable value in estimating the degree of arterial spasm or arterial insufficiency in an extremity, whereas in the chapter entitled "Examination of the Patient" the test is stated to be unreliable and, if used alone, to be misleading. In one chapter it is stated that in determining whether or not the pulse cannot be felt because of spasm or organic (thrombotic) occlusion, it is far better to examine the pulse by means of an oscillometer than by other means, such as palpation, whereas in the chapter entitled "Examination of the Patient" it is said emphatically that oscillometry cannot distinguish between spastic and organic disease.

In the chapter "Senile Obliterative Arteritis" it is implied that sympathectomy for the relief of intermittent claudication is advisable for many patients with occlusive arterial disease and that the results are good in 60 per cent of the patients, whereas in the chapter "Sympathetic Innervation of the Peripheral Blood Vessels" it is questioned that sympathectomy is of value in the relief of intermittent claudication and it is stated that the procedure is not indicated for intermittent claudication alone in patients with occlusive arterial disease.

Despite these criticisms the volume contains up-to-date information about many subjects of current interest in the field of vascular disorders.

Some of the chapters in the book are outstanding, including the chapters entitled "Physiology of Sympathetic Innervation of Peripheral Blood Vessels," "Examination of the Patient," "Thromboangiitis Obliterans," "Raynaud's Disease and Raynaud's Phenomenon" and "Anticoagulant Therapy," to mention only a few. The presentation of technic in the chapter entitled "Angiology" is superb and has an appropriately conservative attitude as to the routine use of these technics. Consideration of the diagnostic application of peripheral angiography as related to treatment could have been more detailed, especially in regard to the newer technics of arterial grafting and bypass operations.

The publishers have done an excellent job in producing the book. The illustrations in the main are very clear and the type is easily readable. This is not a book to be recommended as a whole for the medical student or general physician or surgeon inexperienced in the field of vascular diseases, because of the sections of the book that are not in accord with modern and generally accepted concepts of peripheral vascular diseases and that require critical evaluation by the reader.

EDGAR A. HINES, JR.

Diseases of the Heart. Ed. 2. *Charles K. Friedberg.* Philadelphia, W. B. Saunders Co., 1956, 1161 pages, 157 figures. $18.00.

The gratifying progress in our knowledge of cardiovascular disease is reflected vividly in the speed with which textbooks are outdated. The second edition of Friedberg's *Diseases of the Heart,* appearing after an interval of only 7 years, necessitated extensive rewriting of almost every chapter. Part I consists of 3 new chapters on graphic methods of cardiac examination. These include discussions of roentgenologic examination of the heart, angiocardiography, electrocardiography, vectorcardiography, ballistocardiography, phonocardiography, and cardiac catheterization. These technics are clearly described with particular reference to the normal. They thereby provide orientation for the discussions throughout the book of these methods as they are related to cardiovascular disease.

Discussion of the various aspects of heart disease is comprehensive and detailed. The sections on congestive heart failure, angina pectoris, acute coronary occlusion, and myocardial infarction constitute excellent monographs. Certain special problems of the circulation are reviewed with admirable critique. These include the heart in hyperthyroidism, the heart and circulation in myxedema, traumatic heart disease, cardiac tumors, pregnancy and heart disease, and management of cardiac patients requiring major surgery.

This text is remarkable in combining in proper balance, the pathologic physiology, pathology, and clinical signs and symptoms of heart disease. The style is simple and clear. Extensive bibliographic references follow each of the 49 chapters. The book is an outstanding accomplishment and is strongly recommended to all physicians.

HERRMAN L. BLUMGART

Radicular Syndromes. With Emphasis on Chest Pain Simulating Coronary Disease. *David Davis.* Chicago, The Year Book Publishers, Inc., 1957, 266 pages, 69 figures. $6.50.

The differential diagnosis of chest pain is an ever-present problem, and frequently a perplexing one. One aspect that is often overlooked is the radicular syndrome with symptoms that closely simulate those of coronary artery disease.

In this text the author describes cervical and upper thoracic root syndromes in considerable detail and with an abundance of case illustrations. Starting with the historical background, he carefully develops the concept of root syndromes and reviews the mechanics, nerve supply, and segmental patterns. There is a thorough section on diagnostic signs and a brief review of the roentgenologic aspects. The case histories illustrate symptoms that are due to root compression but that could easily be mistaken for those of frank coronary artery disease, or, in some instances, could be due to pulmonary or cerebral involvement. One very important point that the author stresses is the possible co-existence of root compression and active coronary artery disease. Spinal tenderness is very frequent in chest pain of root origin and thus serves as a most useful sign.

The diagnostic and therapeutic importance of traction is described throughout the text. The last section describes other or concomitant forms of therapy, such as exercises and postural correction, as well as a more detailed description of traction.

This book should increase the awareness of chest pain that may be due to cervical or thoracic root compression and is recommended to those who should be interested in this phenomenon.

LEONARD H. SCHUYLER

Synopsis of Pathology. Ed. 4. *W. A. D. Anderson.* St. Louis, The C. V. Mosby Co., 1957, 829 pages, 328 figures, 12 color plates. $8.75.

This is a carefully revised edition of an unusually popular summary of the subject of pathology. It is such a well written and complete

synopsis of the subject that many medical students read only this book. This is the fault of the student. The text is the longest and the number of figures the largest of the 4 editions. Some old figures have been omitted, new ones substituted, and a few added. There has been a striking improvement in the quality of the reproduction of these figures, even of the old ones, perhaps due in part to the improvement of the quality of the paper. For a rapid survey of the subject this book can be recommended highly, and the reviewer predicts that the continued demand for the book will insure new editions for many years to come.

HARRY GOLDBLATT

The Coronary Club. A Cheerful Tale. *Herbert Faulkner West.* Hanover, New Hampshire, Westholm Publications, 1956, 45 pages.

This is a personal account by a college instructor of his subjective, factual, and spiritual experiences in an attack of acute myocardial infarction. For the physician it will afford insight into the psychologic reverberations of the illness on an intelligent patient. For the reader, whether or not a physician, it will also evoke admiration for the author, for this delightful tale reveals gallantry, wisdom, wit, modesty, and the literary ability to express his inherent qualities. These 45 pages contain high humor, deep tragedy, succinct reflections on life and death, and delightful reflections on the art of painting.

HERRMAN L. BLUMGART

Röntgenologische Funktionsdiagnostik. Mittels Serienaufnahmen und Kinematographie. *Robert Janker.* 2 volumes. Bonn, W. Girardet, 1956. DM 39.

In this liberally illustrated book the author discusses the methods and apparatuses used for direct and indirect rapid serial and cinematographic radiography as developed and used by the team of radiologists, internists, and surgeons at the Bonn Clinics. The special part deals first with the application of these methods in the intestinal and respiratory tract; the cardiologist, however, will be interested mainly in their use for the cardiovascular system.

It is advisable to have fluoroscopic facilities during the performance of angiocardiography. The immediate observation during injection gives evidence of success or failure of the examination so that, in the favorable case, one has not to leave the needle or catheter in place until the films are processed. In extremity angiography, arteriography as well as venography, film succession in 1-second intervals is appropriate. For angiocardiography no fewer than 3 frames per second should be used. If the indirect method (photography of the screen image) is used, a 70-mm. film is preferable to the 35-mm. film because of greater detail. For angiocardiography the author's team uses Perabrodil M (Bayer) 80 per cent (corresponding to U.S.A. Diodrast) to a maximum dose of 50 ml. This review is confined to these few statements because the treatise deals mainly with radiologic methodology and uses clinical examples only for illustration and evaluation of different technics.

FELIX G. FLEISCHNER

Roentgen Signs in Clinical Diagnosis. *Isadore Meschan.* Philadelphia, W. B. Saunders Co., 1956, 1058 pages, 2216 illustrations. $20.00.

This book offers an interesting approach to the study of roentgenology. The presentation incorporates detailed normal radiographic anatomy, the roentgen signs that involve basic concepts of roentgen pathology, and the clinical possibilities that may be interpreted from the film. Throughout there are many excellent diagrams, illustrations, and film reproductions. In addition, the book is quite comprehensive, including most disease complexes seen in a busy hospital and also some of the rare oddities. It is so all-inclusive that it perhaps loses some of its teaching value as a text for medical students but not for residents in radiology. It would, however, be attractive to general practitioners who do not have access to a trained radiologist. Included are short chapters on radiographic technic, physics, and radiation protection. Approximately one third of the text is devoted to the skeletal system, of special interest to the orthopedic surgeon. The chapters concerning the lungs and mediastinum are commendable in that they include some of the newer concepts of pulmonary parenchymal and vascular disease.

Of special interest to the cardiologist are 2 relatively short chapters, "The Radiography of the Heart," and "Congenital Heart Disease." The author describes in detail the radiographic anatomy of the cardiac silhouette as usually seen on the conventional views of the chest. These are excellently illustrated by diagrams. Included are comprehensive paragraphs on cardiac mensuration and the factors that influence it. The short chapter on congenital heart disease is a good basic outline. The final chapters of the book are of interest to the urologist, gastroenterologist, and gynecologist.

The author has made a valuable contribution to those interested in roentgenology, particularly residents in radiology.

ARNOLD L. BERENBERG

ABSTRACTS

BLOOD COAGULATION AND THROMBOEMBOLISM

Chevalier, H.: Treatment of Severe Pulmonary Embolism. Presse méd. **65**: 156 (Jan. 26), 1957.

The author discusses the pathophysiologic derangements induced by massive pulmonary embolism as a background for therapeutic procedures. Among the noxious factors, the most important are acute pulmonary and right ventricular hypertension, interference with capillary-alveolar gas exchange, reduction of pulmonary venous and left ventricular filling, peripheral vascular collapse and visceral hypoxia. Among secondary factors, the local liberation of serotonin is considered as possibly leading to further vasomotor reactions. Therapeutically, the use of vasopressor amines, particularly norepinephrine and Aramin is recommended. Anticoagulants are advised for prophylaxis. Surgical procedures such as embolectomy and vein ligation have only limited value but are occasionally life saving.

Pick

Tricot, R., Chiche, P., and Acar, J.: Canalized Thrombus of the Left Auricle. Arch. mal. coeur **50**:75 (Jan.), 1957.

A 39-year-old woman showed intense cyanosis, fever and rapidly progressive right ventricular failure; the electrocardiogram showed atrial fibrillation and tall R waves without S waves in V_{1-3}. No diastolic murmur could be heard. Autopsy disclosed a very tight mitral stenosis and an organized thrombus of the entire left atrial appendage and part of the atrium, 9 by 6 cm. in dimensions. The thrombus was transfixed by 2 canals continuing the course of the left pulmonary veins, and 2 indentations continuing the course of the right pulmonary veins; it did not adhere to the atrial wall.

Lepeschkin

O'Brien, J. R.: Some Postprandial Effects of Eating Various Phospholipids and Triglycerides. Lancet **1**:1213 (June 15), 1957.

The changes in the Russell-viper-venom accelerated clotting time (Stypven time) of platelet-poor plasma and the plasma fatty acid, cholesterol, and phospholipid were measured after meals containing various lipids. Four fats shortened the postprandial Stypven time. The degree of unsaturation was not significant in affecting clotting but the length of the fatty acid chain seemed important. Ingested phospholipid was more effective than triglyceride but its effectiveness bore no relation to its activity in an in vitro test system of plasma and venom.

Kurland

Warren, R., and Belko, J. S.: A Comparison of Heparin and Bishydroxycoumarin (Dicumarol) as Anticoagulants. Resistance to Tissue Thromboplastin. Arch. Surg. **74**:50 (Jan.), 1957.

An in vitro test utilizing coagulation and recalcification times was employed to study the resistance to varying amounts of tissue thromboplastin of human blood rendered hypocoagulable, to so-called "therapeutic" levels, by heparin and bishydroxycoumarin. Blood heparinized in vivo to a coagulation time of 30 minutes is more resistant to tissue thromboplastin in a test tube than is blood

Dicumarolized to a prothrombin activity of 10 per cent to 19.9 per cent. Blood heparinized in vitro to a coagulation time of 30 minutes and its resistance to thromboplastin studied by coagulation time was the same as blood Dicumarolized to a prothrombin activity of 10 per cent to 19.9 per cent and studied by plasma recalcification time. If both bloods were studied by the plasma recalcification time, the resistance to thromboplastin was greater in the heparinized blood than in the Dicumarolized blood. In the opinion of the authors, the data suggest that blood with a 30-minute coagulation under heparin is somewhat more effective in resisting thrombosis than is blood Dicumarolized to a level between 10 per cent and 19.9 per cent prothrombin activity. By both coagulation times and plasma recalcification times, heparinized blood with a coagulation time of 30 minutes was found to be markedly superior in anticoagulant effect to Dicumarolized blood with prothrombin activity of 20 per cent to 30 per cent. The amounts of thromboplastin used were arbitrarily chosen and just how closely they approximate the ordinary stimulus to thrombosis in vivo is unknown. Further, both heparinized and Dicumarolized blood remain less coagulable than normal blood even at the highest amount of thromboplastin used. Therefore, despite the evidence suggesting that heparin is a better anticoagulant than bishydroxycoumarin, the authors do not advocate that heparin replace Dicumarol where long-term anticoagulants are needed. They would employ heparin in situations where the choice between heparin and bishydroxycoumarin from the point of view of convenience and duration of anticoagulant administration is equal.

BROTHERS

CONGENITAL ANOMALIES

Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Ebstein's Disease: Description of the Heart of the First Case Diagnosed during Life. Am. J. M. Sc. **233**: 23 (Jan.), 1957.

The authors describe the heart of the first case of Ebstein's disease diagnosed during life. The pathognomonic angiocardiographic feature of Ebstein's disease is the presence of a nonopacified narrow band separating the right atrium and auricularized right ventricle from a diminutive, functioning right ventricle. This narrow band is due to a muscular ridge at the caudal line of fusion of the 3 leaflets of the anomalous tricuspid valve. The enlarged right atrium probably contributes little to the forward movement of blood. Hypoplasia of the right ventricular wall proximal to the anomalous posterior leaflet is an integral part of Ebstein's disease. The major factor producing forward propulsion of blood may be the septal wall, as suggested by the considerable hypertrophy of the septal wall of the heart found by the authors at autopsy.

HARRIS

Bauersfeld, S. R., Adkins, P. C., and Kent, E. M.: Patent Ductus Arteriosus in Infancy. J. Thoracic Surg. **33**: 123 (Jan.), 1957.

The authors analyze the features of patent ductus in 22 infants under the age of 2 years, seen in a 3-year period along with 52 other cases among older children. Nearly all the infants had a history of poor weight gain since birth, and many also had dyspnea or frequent respiratory infections. A continuous murmur was present in 9 of the 22 patients, whereas 12 had only a systolic murmur along the left sternal border. The latter group presented a problem in differential diagnosis, chiefly with respect to interventricular septal defect. In these infants retrograde aortography was preferred to cardiac catheterization because of the greater ease of performing the procedure in such small subjects. The authors believe that the diagnosis of patent ductus should be considered in infants with a systolic murmur and a history of poor weight gain. If there is evidence of cardiac enlargement and increased pulmonary vascularity retrograde aortography is indicated.

ENSELBERG

Kaufman, J. M., Campeau, L. A., Ruble, P. E., Monahan, J., and Dodrill, F. D.: Pregnancy and Successful Delivery in a Case of Tetralogy of Fallot. Arch. Int. Med. **99**: 487 (March), 1957.

A case of surgically treated tetralogy of Fallot with pregnancy, delivery, and uneventful postpartum course is presented. A review of the literature reveals that 3 similar cases have previously been reported. It is suggested that patients with surgically treated tetralogy of Fallot and possibly other cyanotic heart diseases may have normal pregnancy and successful delivery. The essential problems of management are briefly discussed.

BERNSTEIN

Plowman, D. E. M.: Congenital Absence of Spleen Associated with Cardiac Abnormalities. Brit. M. J. **1**: 147 (Jan. 19), 1947.

A male child died at 13 weeks and at autopsy showed a bilocular heart. Each lung possessed 3 lobes. There was no spleen. The pancreas was a small round mass of tissue and the stomach a mere widening of the gut buried in the liver. In life counting white cells the total number of nucleated cells was 19,000 of which 40 per cent were normoblasts. The combination of unusual blood picture with cyanotic heart disease might have

suggested the correct diagnosis. According to the review of the literature in the annotation, symmetrical lobation of the liver and lungs has been frequent. The commonest single cardiac defect seems to be ostium atrioventriculare commune. Putschar and Manion are quoted as pointing out that the spleen is the only strictly unilateral organ in the body. The disturbance in embryonic development seems to be one of development of "laterality." Gasser and Willi are reported as finding Heinz bodies in 10 per cent or more of red cells in splenic agenesis—a potentially useful diagnostic clue. There is insufficient evidence to come to any conclusion about susceptibility to infection in these patients.

McKusick

Loogen, F., and Wolter, H. H.: An Unusual Arterio-Venous Pulmonary Shunt. Ztschr. Kreislaufforsch. **46**: 328 (April), 1957.

A 38-year-old man showed intense cyanosis but no murmurs and only slight lowering of the T wave in lead I and wide P waves in the electrocardiogram. Cardiac catheterization showed very low oxygen saturation and a small effective heart output. The catheter penetrated through the right pulmonary artery into the right atrium, and a communication between these could also be demonstrated by means of angiocardiography. Operative ligation of the communication proved impossible, and the patient died a few hours after the operation. At autopsy the communication was found to be three fingers wide.

Lepeschkin

Kirklin, J. W., Harshbarger, H. G., Donald, D. E., and Edwards, J. E.: Surgical Correction of Ventricular Septal Defect: Anatomic and Technical Considerations. J. Thoracic Surg. **33**: 45 (Jan.), 1957.

This report is based on experience with 36 patients operated upon for repair of ventricular septal defects. Extracorporeal circulation, using a mechanical pump-oxygenator with a Gibbon-type stationary vertical screen oxygenator, permitted the right ventricle to be opened widely. Since this report was prepared the authors have adopted the routine use of potassium-induced cardiac systole in performing these repairs. The types of defects encountered in these 36 patients can be divided into 2 main groups; those related to the outflow tracts and those related to the inflow tracts. The most common site was the right ventricular outflow tract inferior to the crista supraventricularis. These defects may involve the septal tissue just below the aortic annulus. Defects superior to the crista supraventricularis are closely related to the pulmonary valve. In the inflow tract defects are located entirely in the muscular wall in 2 locations; beneath the septal leaflet of the tricuspid valve or in the muscular septum near the apex. Trauma by forceps or needle point, to the remnant of membranous septum at the postero-inferior edge of the defect may result in ventricular standstill or atrioventricular block, indicating that conduction tissue lies in this area. The technic of closure is described, using noncompressed polyvinyl-formal sponge. The over-all incidence of complete repair was 20 out of 36 patients. In the last 25 patients, by the technic mentioned above, complete repair was achieved in 18 patients.

Enselberg

CORONARY ARTERY DISEASE

Wang, H. H., Frank, C. W., Kanter, D. M., and Wégria, R.: An Experimental Study on Intercoronary Reflexes. Circulation Research **5**: 91 (Jan.), 1957.

The observation of Manning, McEachern, and Hall that the mortality following coronary artery ligation was much greater in unanesthetized than in anesthetized dogs, led to the proposal that in the former, the area of myocardium deprived of blood induced a reflex constriction of the coronary bed. The experiments reported herein were performed on anesthetized dogs with continuous measurements of flow in the right coronary, left anterior descending, and left circumflex arteries. When 1 of the arteries was occluded for 1 to 2 minutes, there was no evidence for a reflex constriction of the other two arteries. These experiments do not rule out completely the possibility of reflex constriction because the vessels might have been denervated by the cannulation.

Aviado

Master, A. M., Field, L. E., and Donoso, E.: Coronary Artery Disease and the "Two-Step Exercise Test." New York State J. Med. **57**: 1051 (March 15), 1957.

The results of a systematic investigation of 250 consecutive patients with definite coronary artery disease are reported. Using leads 2, V_3-V_5 or V_4-V_6 in the Master "two-step exercise test," the authors believe an RS-T depression of more than 0.5 mm. in any lead is the criterion of a positive test. Minor T-wave changes alone are of no or little significance, although T-wave inversion is probably abnormal. Transient arrhythmias likewise have little significance. In 142 of the 250 patients the single test demonstrated electrocardiographic evidence of interference with the coronary circulation. In 100 of the 108 remaining patients the single test was negative, but the double test was abnormal. In only 8 instances (3.2 per cent) were both tests normal. A negative double Master "two-

step exercise test" is valuable in diagnosis, since it practically excludes the presence of a disturbed coronary circulation. This test is important in patients whose chest pain is not typically anginal in character and whose resting electrocardiogram is normal or borderline. The Master "two-step exercise test" is only a diagnostic aid and should not be considered the sole diagnostic criterion of coronary disease.

HARRIS

Struppler, A.: Coronary Infarction. Reflex Mechanism or Myocardial Failure? Ztschr. Kreislaufforsch. **46**: 49 (Jan.), 1957.

In 40 cats the right and sometimes the left coronary artery was clamped temporarily while the action potentials of afferent vagal fibers were registered continuously with the electrocardiogram and the arterial and venous pressures. Three-quarters of the animals showed, 5 to 10 seconds after clamping, a fall in arterial pressure and a less pronounced fall in the heart rate; the remaining animals showed tachycardia and transient hypertension. All showed an increase in atrial pressure accompanied by a corresponding increase in the frequency of action potentials from atrial receptors. This reaction was diminished and delayed by respiration of pure oxygen, but was not influenced by bilateral vagotomy. It was therefore held probable that the hypotension and bradycardia accompanying clinical myocardial infarction was not of reflex origin but was caused by myocardial failure.

LEPESCHKIN

Brofman, B. L.: Surgical Treatment of Coronary Artery Disease: Medical Management and Evaluation of Results. Dis. Chest **31**: 253 (March), 1957.

The Beck operation for coronary artery disease is a safe and effective method of providing a more adequate distribution of arterial blood supply to the heart. Operation is indicated in patients with a positive diagnosis of coronary artery disease unless there is a specific contraindication. The operation should not be considered as merely a salvage procedure. Best results are obtained by operating early in the course of the disease. The following preoperative classification has been found useful: Group 1. Patients with mild symptoms, usually under 50 years of age who may have a small infarct or mild angina. Group 2. Patients with moderate to severe angina who have one or more infarcts and a normal heart size. Group 3. Patients with extensive muscle damage who may have large hearts and congestive heart failure. Patients with status anginosus. Absolute contraindications include acute myocardial infarction and impending infarction. Severe hypertension, or any other associated disease which, per se, limits life expectancy contraindicates operation. Cardiac enlargement and congestive failure constitute relative contraindications. Pre-treatment with antithyroid drugs appeared to decrease significantly the operative risk in the patient with status anginosus or severe anxiety. Prior to surgery all patients were completely digitalized. Following surgery all patients showed a significant rise in serum transaminase, the peak being reached in 48 hours postoperatively. The great majority of patients undergoing operation were in Group 2. In the last 100 patients there has been no operative mortality. The over-all mortality for 225 operated since January 1951 is less than 5 per cent. Long-term follow-up (6 months to 5 years) reveals a significant increase in longevity for operated patients. Furthermore, 90 per cent were back at full-time or part-time work with little or no limitations.

MAXWELL

Bailey, C. P., and Gilman, R. A.: Experimental and Clinical Resection for Ventricular Aneurysm. Surg. Gynec. & Obst. **104**: 539 (May), 1957.

Ventricular aneurysm is caused in most instances by myocardial infarction, and it is of serious import. In a clinicopathologic study, 70 per cent of such patients developed heart failure; and 21 per cent had fatal thromboembolism, the latter apparently arising in the aneurysm.

Ventricular aneurysm excision was undertaken by the authors to do away with a thrombogenic focus and also in an effort to improve ventricular function. The operative technic and its experimental application in dogs are described. Seven of 8 patients survived the operation; the one fatality was attributed to embolism from the dislodgment of an intraaneurysmal thrombus during surgical manipulation. Follow-up data in the other patients are not given. It is concluded that the dismal outlook in ventricular aneurysm medically managed strongly suggests a more aggressive (surgical) treatment of the lesion.

ROGERS

Lewitus, Z., and Neumann, J.: On the Distribution of Coronary Thrombosis Attacks. A Statistical Analysis of 396 Cases. Am. Heart J. **53**: 339 (March), 1957.

The authors report a statistical analysis of 396 proved cases of first and recurrent myocardial infarction among the members of the Sick Fund of Jewish Labour in Israel who were hospitalized at the Beilinson Hospital during the period of January 1, 1949, to June 30, 1953. Since the cases followed a Poisson distribution, the results of

is study suggest that the incidence of myocardial infarction is of random nature and not influenced by any weather condition.

SAGALL

Weinreb, H. L., German, E., and Rosenberg, B.: A Study of Myocardial Infarction in Women. Ann. Int. Med. **46**: 285 (Feb.), 1957.

The major clinical features in a series of 231 women with proved myocardial infarctions are described. The group as a whole showed an increased frequency of diastolic hypertension. (51.5 per cent), diabetes mellitus (52.6 per cent), an elevated serum cholesterol (44.3 per cent). A positive family history of diabetes, hypertension, or coronary artery disease was present in more than two-thirds of the patients. A strikingly poorer prognosis was noted among the women with diabetes than among the nondiabetic women. Of 156 patients about whom information was available, 13.5 per cent had neither diabetes nor hypertension. Of the 23 women in this group under the age of 50 years, 26.1 per cent had neither disease. Only 2 women, both under 50 years at the time of their first myocardial infaret, did not have diabetes, hypertension, hypercholesteremia, or a positive family history. Coronary artery disease must be seriously considered in women presenting a suggestive clinical picture, particularly in the younger age group, despite the absence of hypertension or diabetes mellitus. Electrocardiographically, the infarcts were localized to the anterior portion in 49 per cent, to the posterior portion in 44.3 per cent and the remainder were septal, high lateral, or anterior and posterior in combination. No conclusions could be made relative to the influence of oophorectomy relative to the occurrence of myocardial infarction. The data in this series indicated that diabetes mellitus was a particularly important factor predisposing to the occurrence of myocardial infarction in women. Hypertension and elevated blood cholesterol values have played apparently a less significant role. In the opinion of the authors, the lipoid alterations and the hypertensive tendency which are noted in diabetics cannot completely explain the relationship between diabetes and myocardial infarction.

WENDKOS

Lieberman, J., Lasky, I. I., Dulkin, S. I., and Lobstein, O. E.: Serum Glutamic-Oxalacetic Transaminase Activity in Conditions Associated with Myocardial Infarction. II. Cerebral Vascular Accidents and Congestive Heart Failure. Ann. Int. Med. **46**: 497 (March), 1957.

The response of serum glutamic-oxalacetic transaminase (SGO-T) activity was studied in conditions likely to be associated with myocardial infarction, i. e., cerebral vascular accidents and right heart failure. Of 21 patients with a diagnosis of recent cerebral vascular accidents, 3 had underlying myocardial infarctions, and 9 showed significant elevation of SGO-T activity with no evidence of cardiac involvement. SGO-T elevation occurred most frequently in cases of severe cerebral vascular accident, with curves resembling those of myocardial infarction except for a more gradual initial rise in activity. Hemorrhages and thromboses resulted in approximately equal elevations. It appears that the SGO-T activity determination is of limited value in the diagnosis of myocardial infarction when the picture suggests a severe, primary cerebral vascular accident.

In 11 out of 14 patients with moderate to severe right heart failure, there was no elevation of SGO-T activity, although 3 of these patients demonstrated a gradual drop of over 15 units in their "normal" levels with the attainment of compensation. Three patients demonstrated definite SGO-T elevation, which remained unexplained. Right heart failure is only infrequently a complication of myocardial infarction. However, congestion of the liver may have to be considered in evaluating the SGO-T test when symptoms of myocardial infarction appear in patients already in congestive heart failure. Ordinarily, the presence of failure does not interfere with the interpretation of the SGO-T test in individuals with possible myocardial infarction.

WENDKOS

Lieberman, J., Lasky, I. I., Dulkin, S. I., and Lobstein, O. E.: Serum Glutamic-Oxalacetic Transaminase Activity in Conditions Associated with Myocardial Infarction. I. Bodily Trauma. Ann. Int. Med. **46**: 485 (March), 1957.

The activity of glumatic-oxalacetic transaminase (SGO-T) was studied in 51 persons with body injury to establishing the value of such determinations as a diagnostic test for myocardial infarction in cases of trauma with symptoms which suggest the presence of cardiac injury as well. The patients studied were victims of a variety of accidents admitted to the Harbor General Hospital in California. No elevation of serum-glutamic-oxalacetic transaminase activity was found in 27.5 per cent, whereas this enzyme was elevated in the blood in 72.5 per cent. In 17.7 the elevation was associated with evidence of cardiac trauma. In 55 per cent there was an elevation of this enzyme without evidence of cardiac trauma. In this last group the maximum value for transaminase activity was between 43 and 515 units. In the majority of cases the elevation was explainable by the damage to the skeletal muscle.

In the majority of the cases (70.8 per cent) the transaminase activity rose rapidly and attained a maximum level between the first and the second days after the injury and returned subsequently to normal values in the course of variable periods of time. In 29.2 per cent the transaminase activity rose less rapidly and attained its maximum level between 3 and 6 days. On the basis of these observations it appears that an elevation of activity of transaminase is to be expected in an individual who has suffered moderate or severe body injury. It is concluded that SGO-T activity cannot be used as a specific test of cardiac injury in accident victims, since over 50 per cent of the injured patients tested showed elevated SGO-T activity unrelated to demonstrable cardiac injury.

WENDKOS

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Horan, J. M.: Acute Staphylococcal Pericarditis. Pediatrics **19**: 36 (Jan.), 1957.

This article reports 2 cases of acute staphylococcal pericarditis in infants, and reviews a series of 27 cases of nontuberculous pericarditis in patients under 20 years of age seen at the Charity Hospital in New Orleans. The organism causing the pericarditis varied, but the commonest was *Staphylococcus aureus,* accounting for 15 of the 27 cases. Usually the pericarditis was part of a generalized infection; septicemia was present in 14 of the children. Staphylococcal pneumonia was the commonest associated lesion, and osteomyelitis second. Diagnosis was difficult, for symptoms are not specific in childhood and reliance must be on physical signs. These were usually cardiac enlargement, a friction rub, or electrocardiographic changes. In general, the courses of these patients fell into 2 patterns. One group showed an acute fulminating disease, primarily bacteremia with multiple systemic abscesses leading rapidly to death. The other group appeared to have some resistance and infection was confined to 1 area, with either pericarditis or osteomyelitis as the main manifestation. The mortality rate was extremely high. Survivors received penicillin or broad spectrum antibiotics, combined with pericardial drainage as definitive therapy. Because of the relative resistance of the organisms to penicillin, the author believes that a broad spectrum antibiotic such as chloramphenicol should be used along with the penicillin until reports on the sensitivity of the organism have been obtained from the laboratory. The author pleads for earlier diagnosis by means of a higher index of suspicion.

HARVEY

Costeas, F., Yatzidis, H., Coidakis, A., and Michaelides, G.: Cholesterologenic Pericarditis. A Complete Anatomo-Clinical Study. Presse méd. **65**: 336 (Feb. 20), 1957.

A new case is presented of chronic constrictive pericarditis resulting from deposition of large masses of cholesterol crystals demonstrated at autopsy. The clinical features were unusual in that the process developed within 4 months, repeated pericardial taps invariably were followed by shock and injection of streptomycin into the pericardial sac lead to hemorrhagic exudation. The roentgenogram showed a localized left-sided enlargement of the heart shadow resembling a cardiac tumor rather than a pericardial process, and the electrocardiogram failed to show evidence of myocardial involvement. As in previously reported cases, the actual cause for the accumulation of cholesterol masses in this particular location remained obscure.

PICK

de Vernejoul, R., Buisson, P., Courbier, R., and Tricot, R.: Post-traumatic Constrictive Pericarditis. Presse méd. **65**: 241 (Feb. 9), 1957.

On the basis of 1 personal observation and 25 cases collected from the literature, the authors studied the role of trauma in the etiology of constrictive pericarditis. Close similarity was found in the reaction of pleural and pericardial serous membranes with regard to the response to various types of injury, the development of secondary infection and the ultimate outcome in a constrictive process. The importance of prophylactic treatment consisting in prompt evacuation of blood collecting in the pericardial cavity is emphasized. Once pericardial constriction has developed, the therapy is pericardectomy performed as completely as possible.

PICK

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Fleming, P. R., and Muir, F. H.: Electrocardiographic Changes in Induced Hypothermia in Man. Brit. Heart J. **19**: 59 (Jan.), 1957.

The authors report the electrocardiographic changes, primarily in lead II, which occurred in 29 patients while under hypothermia for surgery. All showed progressive bradycardia with fall in temperature. Rare ventricular and frequent atrial premature beats with wandering pacemaker were seen. Subsequent atrial fibrillation was common. Patients with atrial fibrillation had a lower mortality than those who remained in sinus rhythm.

ventricular fibrillation occurred in 21 frequently without warning and nearly always in association with manipulation of the heart or great vessels. The P-R interval was prolonged but only slightly. Prolongation of the QRS interval was more consistent and above normal in 13. Prolongation of the S-T interval was most constant and may be 30 to 70 per cent above normal. The most striking feature was the appearance of an injury current present in 6 and followed by atrial fibrillation in 5.

SOLOFF

Whitfield, A. G. W., and Kunkler, P. B.: Radiation Reactions in the Heart. Brit. Heart J. **19**: 53 (Jan.), 1957.

The authors describe 4 patients in whom the T waves, primarily in the right precordial leads, turned negative without cardiac symptoms during or following radiotherapy to the thorax and returned to normal in 3 within weeks of the conclusion of radiotherapy. The fourth died while the T waves were still abnormal. No cardiac cause of death was found. The authors believe that the T-wave changes are due to radiation effects on the heart.

SOLOFF

Horan, L. G., Burch, G. E., and Cronvich, J. A.: A Study of the Influence upon the Spatial Vectorcardiogram of Localized Destruction of the Myocardium of Dog. Am. Heart J. **53**: 74 (Jan.), 1957.

The results of electrocardiographic and spatial vectorcardiographic studies following acute localized myocardial destruction in 27 dogs are reported. The myocardial damage was produced in some of the dogs by burning with a soldering iron, acetylene torch, or electrocautery; in others, by ligation of one or more branches of the left coronary artery; and in the remaining group by the instillation of formaldehyde into the pericardial cavity. The effect on the QRS·Ê loop of superficial localized myocardial destruction was either not detectable or, more often, led to the appearance of a small deformity in the direction predicted by present-day electrocardiographic concepts. Similarly, shifts in S-T vectors and orientation of T·Ê loops, when recorded, were in the predicted direction.

SAGALL

Herrmann, G. R., Oates, J. R., Runge, T. M., and Hejtmancik, M. R.: Paroxysmal Pseudoventricular Tachycardia and Pseudoventricular Fibrillation in Patients with Accelerated A-V Conduction. Am. Heart J. **53**: 254 (Feb.), 1957.

Six cases of pseudoventricular rhythms (2 of tachycardia and 4 of fibrillation) in patients with the so-called Wolff-Parkinson-White syndrome of short P-R intervals and slurred-up R delta waves, slightly broad QRS complexes in the standard and in the precordial leads are reported. The extremely rapid heart action, regular or irregular, of over 200 per minute in young patients in whom pulses were visible and audible and in whom the blood pressure was maintained suggested paroxysmal atrial tachycardia or fibrillation with accelerated atrioventricular conduction as the basic rhythm rather than a true ventricular source. The diagnosis of pseudoventricular tachycardia was indicated in the electrocardiogram by the presence of a high grade regular tachycardia with false bundle-branch complexes with regularly placed P waves on each broad QRS, and occasionally a few narrow complexes. The diagnostic criteria of pseudoventricular fibrillation due to atrial fibrillation with false bundle-branch block include paroxysms of an absolutely irregular rhythm with no P waves and occasional short runs of narrow QRS intervals and very high ventricular rates of over 200. The prognosis in these patients is good but in a rare case the patient has died in an attack. The drug of choice appears to be procaine amide in 0.25- to 1.0-Gm. doses intravenously, up to 2 Gm. in 24 hours. It should be given slowly with constant electrocardiographic monitoring and frequent blood pressure determinations and stopped after conversion of the disorder or when toxic broadening of the QRS intervals appear or if the blood pressure drops significantly.

SAGALL

Burger, H. C.: A Theoretical Elucidation of the Notion "Ventricular Gradient." Am. Heart J. **53**: 240 (Feb.), 1957.

The author presents a mathematical analysis and derivation of the ventricular gradient. He concludes that in simple cases it can be shown, theoretically, that the ventricular gradient is independent of the point of excitation and can be expressed in the gradient of the time interval between depolarization and repolarization.

SAGALL

Robertson, D.: On Consistency in Convention of "View" in Vectorcardiography. Am. Heart J. **53**: 247 (Feb.), 1957.

The author presents a critical review of polarity conventions in vectorcardiography. He points out the confusions that have resulted because of varied representations of vectorcardiograms in different planes and also that some authors' conventions are not consistent with those laid down by Einthoven. Since the movement of the cardiac impulse (represented by a vector) toward the ob-

server is considered to be positive in sign, he argues that in vectorcardiography the frontal plane should be regarded as from the "front"; the sagittal plane should be regarded as from the "left"; the horizontal (coronal or transverse) plane should be regarded as from "below"; and horizontal plane vectorcardiograms should be depicted with their anterior aspect shown at the top of the diagram, viewed as from below.

SAGALL

Rodbard, S., Rubinstein, H. M., and Rosenblum, S.: Arrival Time and Calibrated Contour of the Pulse Wave, Determined Indirectly from Recordings of Arterial Compression Sounds. Am. Heart J. **53**: 205 (Feb.), 1957.

The authors demonstrate in this study in normal human beings that the recording of the arterial sounds commonly utilized in the measurement of the blood pressure on a phonocardiogram simultaneously with an electrocardiogram allows for the construction of a calibrated ascending limb of the arterial pulse wave as well as providing a measure of the time of arrival of the pulse wave at the artery and of the relative rates of transmission of the wave. These data, the obtaining of which previously required intra-arterial puncture, have value in diagnosis and in the assay of procedures and drugs affecting hemodynamic states. By intra-arterial puncture technics, the Q-K time (the interval from the onset of the QRS complex until the registration of the onset of the sound at the brachial artery) was shown to be related to the arrival time of the pulse wave at the artery under the cuff. The Q-K time also was found to be unaffected by changes in the blood flow through the extremity compressed by the cuff, but to be shortened and the slope of the upstroke of the pulse wave to be made more steep by generalized exertion, epinephrine, and norepinephrine. Analysis suggested that these latter changes might be manifestations of an increase in pulse-wave velocity.

SAGALL

Milnor, W. R., and Bertrand, C. A.: The Electrocardiogram in Atrial Septal Defect. A Study of Twenty-four Cases, with Observations on the RSR′-V1 Pattern. Am. J. Med. **22**: 223 (Feb.), 1957.

In 24 patients with uncomplicated atrial septal defects, 6 persistent ostium primum and 18 ostium secundum, the electrocardiographic findings were correlated with the location and size of the defect, the degree of pulmonary hypertension, and the ratio of pulmonary to systemic blood flow. Left axis deviation and signs of left ventricular hypertrophy in 3 patients indicated a persistent ostium primum with cleft mitral valve and mitral insufficiency. In 18 of the remaining 21 patients without left ventricular enlargement, right axis deviation and right ventricular hypertrophy appeared. In 15 patients (63 per cent) there was an RSR′ pattern in lead I but in only 2 was QRS prolonged beyond 0.12 second. The increased incidence of QRS duration in the "high normal" range in patients with RSR′-type and right ventricular hypertrophy suggests that a conduction defect may play a part in its pathogenesis. No useful correlation was found between electrocardiograms and pressure-flow measurements. Prolongation of the P-R interval was present in 4 of 6 patients with persistent ostium primum but in only 2 of 18 with persistent ostium secundum.

KURLAND

Harris, T. N., Saltzman, H. A., Needleman, H. L., and Lisker, L.: Spectrographic Comparison of Ranges of Vibration Frequency among Some Innocent Cardiac Murmurs in Childhood and Some Murmurs of Valvular Insufficiency. Pediatrics **19**: 57 (Jan.), 1957.

The evaluation of cardiac murmurs in childhood is difficult because there is frequent occurrence of innocent murmurs. A study is presented to define some of the physical characteristics of major groups of organic and innocent cardiac murmurs in children. The 2 major innocent murmurs are the "twang-string murmur" and the "pulmonic systolic murmur." Spectrophonocardiographs were made of children with organic valvular disease and with innocent murmurs. The frequencies of vibration of these murmurs were determined. The innocent murmurs of childhood had frequencies the upper limits of which were 370 cycles per second. The groups of organic murmurs had maximum frequencies ranging from 800 to 1300 cycles per second.

HARVEY

Silverblatt, M. L., Rosenfeld, I., Grishman, A., and Donoso, E.: The Vectorcardiogram and Electrocardiogram in Interatrial Septal Defect. Analysis of 30 Cases. Am. Heart J. **53**: 380 (March), 1957.

The authors present a study of the electrocardiograms and vectorcardiograms of 30 well-authenticated cases of interatrial septal defect. In 18 patients the right-sided precordial leads showed an rSR′ configuration. In 5 this pattern was due to complete right bundle-branch block; in 9 to incomplete right bundle-branch block; in 3 to incomplete right bundle-branch block with right ventricular hypertrophy; and in 1 was associated with a QRS duration of less than 0.08 sec

d. In the remaining 12 non-rSR′ records, 10 owed evidence of right ventricular hypertrophy, was compatible with the presence of combined ntricular hypertrophy and 1 was electrocardio- aphically normal. In 29 out of the 30 cases ght ventricular preponderance was revealed by e vectorcardiogram and 4 types of spatial QRS ops characteristic of this preponderance were scribed. No constant relationship between right ntricular pressures and electrocardiographic or ctorcardiographic patterns was found, but the atients with rSR′ configurations were found to ave a lower average systolic pressure in the ight ventricle than the non-rSR′ group. Axis devi- tion was not a reliable index of the degree of ight ventricular hypertrophy and was not found o vary consistently with changing right ventricu- ar systolic pressure.

SAGALL

Evans, W., and Lloyd-Thomas, H. G.: The Syndrome of the Suspended Heart. Brit. Heart J. **19:** 153 (Apr.), 1957.

The authors describe an electrocardiographic abnormality, recorded in the recumbent position, in 13 persons with healthy hearts. This abnormality consisted of depression of ST_3 and to a lesser extent of ST_2, ST_{avf}, and ST_{cr_2} not influenced by posture or exercise. R_2 was taller than R_3, which was taller than R_1. All of these persons had a characteristic cardiac silhouette. In the anterior view, on deep inspiration, the left costophrenic junction moved to the left and the inferior vena cava was exposed on the right as the heart and the diaphragm parted, which was even better seen in the right oblique position. In the left oblique view, the heart appeared suspended by the great vessels above and anchored below by the inferior vena cava. This electrocardiographic and radiologic combination is called the syndrome of the suspended heart. It is important that this electrocardiographic component should not be regarded as a sign of heart disease even if the patient complains of chest pain.

SOLOFF

Bialostozky, D., Wachtel, F. W., Grishman, A., and Donoso, E.: The Correlation Between the Vectorcardiogram and Post-Mortem Findings in Right Ventricular Hypertrophy. J. Mt. Sinai Hosp. **14:** 105 (March-April), 1957.

This study was based on 16 patients with unilateral right ventricular hypertrophy substantiated by pathologic examination. The ages ranged from 7 weeks to 65 years, and etiologies were congenital, pulmonary and rheumatic heart disease. Vectorcardiograms based on the cube system were characteristic of right ventricular hypertrophy in every case. The QRS loops were mainly directed anteriorly, more to the right than normal, and either superiorly or inferiorly. In the horizontal plane the QRS loops were inscribed in the clockwise direction (types I and II), figure-of-eight (type III), or counterclockwise (type IV). In this series of cases the electrocardiograms revealed right ventricular hypertrophy in 14. The authors believe that this study emphasizes the validity of the cube system of spatial vectorcardiography in the diagnosis of right ventricular hypertrophy. It also demonstrates the usefulness of the electrocardiographic criteria employed.

ENSELBERG

HYPERTENSION

Burgison, R. M., O'Malley, W. E., Heisse, C. K., and Krantz, J. C., Jr.: Pharmacologic Studies with 8- (Para-Aminobenzyl)-Caffeine and Certain Related Compounds. J. Pharmacol. & Exper. Therap. **119:** 107 (Jan.), 1957.

This derivative of theophylline elicited a pronounced depressor effect in dogs without decreasing renal blood flow. Cardiac output was increased, so that the cause for the hypotension was entirely systemic vasodilatation. This compound is being tried clinically for its hypotensive effect, particularly because of its good oral absorption.

AVIADO

Evans, W., Short, D. S., and Bedford, D. E.: Solitary Pulmonary Hypertension. Brit. Heart J. **19:** 93 (Jan.), 1957.

The authors describe the clinical findings and those at necropsy of 11 patients with solitary pulmonary hypertension. All were females and all but 1 was under 40 years at death. The first and dominant symptom was dyspnea, which progressed rapidly. Six had associated angina and 5 syncope. Cyanosis was a late finding and was due to a low cardiac output and polycythemia posssibly originating from bronchopulmonary shunts. Clubbing was absent. All had sinus rhythm, right ventricular hypertrophy, and an accentuated pulmonic second sound. A triple rhythm was audible in 6 and at times a systolic apical murmur was present. Catheterization revealed a high pulmonary artery and a normal pulmonary capillary pressure and a low cardiac output. Radiologic examination revealed enlargement of the right heart, dilatation of the pulmonary artery, and oligemic lungs. The average span of life after the onset of symptoms was 2½ years. Necropsy confirmed the presence of cardiac hypertrophy due predominantly to the right heart. The pulmonary artery trunk and its main branches were dilated. Pul-

monary thrombosis may be present. The pulmonary arteriogram clearly portrayed the seat of narrowing or occlusion and the peripheral branches had a pruned appearance. Bronchopulmonary communications were seen. The most significant histologic finding was in the muscular arteries and arterioles, where an obstructive intimal proliferative reaction was present. At these sites the medial coat was hypoplastic or aplastic. At times this type of hypoplasia was present without intimal hyperplasia suggesting an achalasia of the muscular arteries.

SOLOFF

Dahl, L. K.: Evidence for an Increased Intake of Sodium in Hypertension Based on Urinary Excretion of Sodium. Proc. Soc. Exper. Biol. & Med. **94**: 23 (Jan.), 1957.

Among 28 subjects with and without hypertension, the group with high blood pressure had significantly greater sodium intake (as measured by urinary outputs) than the group of nonhypertensives. This observed difference is believed to be unrelated to variations in sodium sweat, since both groups had sendentary occupations. The correlation between high-salt intake and hypertension does not necessarily establish the dependency of one on the other but such a cause-effect relationship is heavily implicated.

AVIADO

Duff, R. S.: Adrenaline Sensitivity of Peripheral Blood Vessels in Human Hypertension. Brit. Heart J. **19**: 45 (Jan.), 1957.

The blood flow in both hands of 39 normotensive and 25 hypertensive patients was measured separately after the injection into 1 brachial artery of minute amounts of epinephrine insufficient to cause either symptoms or perceptible effects on the heart or blood pressure. The same concentration of epinephrine tended to constrict the hypertensive patients more. The degree of sensitivity was generally related to the severity of the hypertensive process. The reaction of some benign hypertensive patients fell within the normal range and the greatest sensitivity to epinephrine was found in those with malignant hypertension.

SOLOFF

de Graeff, J.: Inulin Space and Total Exchangeable Sodium in Patients with Essential Hypertension. Acta med. scandinav. **156**: 337 (Jan. 15), 1957.

This study was concerned with the measurement of total exchangeable sodium in normotensive and hypertensive subjects with radioactive sodium-24 and the determination of extracellular space in the same subjects by the inulin method. Subjects with cardiac or renal disease or other disorders capable of altering water and sodium distribution were excluded. The mean plasma sodium concentration and ratio between inulin space and sodium space were essentially the same in normotensive men and women. There was no clear evidence of enlargement of the inulin space nor an increase of total exchangeable sodium in patients with essential hypertension. The author points out that a major difficulty in studies of water and sodium metabolism is the lack of a satisfactory reference point for the expression of body compartments. The use of the fat-free body as a reference point would solve this problem but there is no satisfactory method for its measurement at the present time. Measurement of the extracellular space also presents difficulties, since the inulin space appears to be smaller than the true extracellular space and it is not certain that the percentage of the true space measured by the inulin method is the same under normal and pathologic conditions. The author points out that a more dynamic investigation of water and sodium metabolism in human essential hypertension, such as study of comparative responses of normal hypertensive subjects to salt restriction may be a more profitable line of investigation.

ROSENBAUM

Cone, T. E., Jr., Allen, M.S., and Pearson, H. A.: Pheochromocytoma in Children. Report of Three Familial Cases in Two Unrelated Families. Pediatrics **19**: 44 (Jan.), 1957.

A detailed case report is presented of a 6-year-old boy with symptoms of a pheochromocytoma cured by surgical removal of the tumor. A maternal aunt and cousin (mother and son), had had pheochromocytomas with paroxysmal hypertension. In another family pheochromocytomas were also discovered in 2 female siblings aged 8 and 6 respectively. Subsequent to successful surgical removal of the tumors in the children, the identical diagnosis was made in the mother in whom pheochromocytomas were also demonstrated at the time of surgery. Pheochromocytoma in childhood is discussed and attention drawn to the familial occurrence of the disease. It is pointed out that sustained hypertension is the rule in childhood with pheochromocytomas. Further, the organs of Zuckerkandl are commonly the site of tumors in childhood. The chief diagnostic point, the authors believe, is the detection of increased catechol amines either in the blood or in the urine. The postoperative management of cases is reviewed.

HARVEY

METABOLIC EFFECTS ON CIRCULATION

Davis, J. O., Pechet, M. M., Ball, W. C., Jr., and Goodkind, M. J.: Increased Aldosterone Secretion in Dogs with Right-sided Congestive Heart Failure and in Dogs with Thoracic Inferior Vena Cava Constriction. J. Clin. Invest. **36**; 689 (May), 1957.

Adrenal vein blood from dogs with right heart failure and from others with constriction of the thoracic inferior vena cava was compared with that of normal controls. Aldosterone activity was increased in both test objects in adrenal venous blood but not in sytemic blood. It is concluded that the increased aldosterone in adrenal vein blood is secreted aldosterone.

OPPENHEIMER

Griffiths, W. J., and Collinson, S.: The Estimation of Noradrenaline in Urine and its Excretion in Normal and Hypertensive Subjects. J. Clin. Path. **10**: 120 (May), 1957.

Because of the complexity of methods presently available for the measurement of urinary catechol amines, this study was undertaken with the object of evolving a relatively simple clinical determination. A fluorimetric method is described for estimation of the total combined epinephrine and norepinephrine in urine based on the ferricyanide oxidation method of von Euler. Comparison of results obtained by bioassay with those of fluorimetry showed no significant difference.

MAXWELL

Jennings, R. B., Kaltenbach, J. P., and Smetters, G. W.: Enzymatic Changes in Acute Myocardial Ischemic Injury. Arch. Path. **46**: 10 (July), 1957.

An experimental study using 21 adult mongrel dogs, 8 serving as controls, in whom homogeneous myocardial infarets were produced in the posterior papillary muscle is presented. The changes that occur, during the first 24 hours after ligation, in the activity and concentration of 3 intracellular enzymes are described. The enzymes studied were glutamic oxaloacetic transaminase (GOT), lactic dehydrogenase (LDH), and succinic dehydrogenase (SDH). After an initial period of little or no decrease in enzyme activity, lasting 40 to 70 minutes with GOT, 2 hours with LDH and 4 to 5 hours with SDH, the tissue levels of all 3 enzymes rapidly decreased until levels of 30 to 50 per cent of normal were reached 12 to 15 hours after ligation. The curve of tissue-enzyme loss is compared to that of an earlier study dealing with potassium loss, and explanations for the various observed time lags are offered.

MAXWELL

PHARMACOLOGY

Farah, A., Rennick, B., and Fraser, M.: The Influence of Some Basic Substances on the Transport of Tetraethylammonium Ion. J. Pharmacol. & Exper. Therap. **119**: 122 (Jan.), 1957.

Earlier attempts to demonstrate inhibition of transport of tetraethylammonium (TEA) ion by basic substances were not successful in the intact dog because in the dosages used these bases produced severe hemodynamic changes that made interpretation of results impossible. Present attempts using dog renal slices showed specific depression of transport of TEA ion by a number of organic bases which are also actively transported by the kidney. The additional evidence presented suggests that this inhibition of TEA transport is of the competitive type.

AVIADO

Aviado, D. M., Jr., and Wnuck, A. L.: Mechanisms for Cardiac Slowing by Methoxamine. J. Pharmacol. & Exper. Therap. **119**: 99 (Jan), 1957.

The baroreceptors in the carotid sinuses and aortic arch are responsible for the major component of the bradycardic responses to intravenous injection of this sympathomimetic drug in anesthetized dogs. When these receptors are selectively denervated, the cardiac slowing is significantly reduced in intensity. The slight bradycardiac response that persists after carotid-aortic denervation is not due to direct action of the drug on the medullary centers, sinoatrial node, or on the coronary and pulmonary sensory receptors (responsible for the Bezold-Jarisch reflex). The remaining alternative explanation is that stretch receptors in the cardiac wall are activated by the rise in atrial and ventricular pressures accompanying the systemic pressor action of methoxamine. The changes in heart rate brought about by this drug are therefore entirely reflex in nature.

AVIADO

Keyl, A. C., and North, W. C.: Cardiac Glycosides in Traumatic Shock. J. Pharmacol. & Exper. Therap. **119**: 229 (Feb.), 1957.

The potassium ion has been implicated in the etiology of shock. Four cardiac glycosides (digitoxin, k-strophanthin, ouabain, and acetyldigitoxin) were found to exert a protective effect against death from tumbling shock in mice. The time course of protection is not similar to the cardiotonic action of the glycosides, but does parallel their effect on serum potassium levels. This is interpreted to indicate that the protective effect of the glycosides is not directly on the heart but upon potassium balance. Available information in the literature indicates that cardiac glycosides govern the rate of potassium re-entry into the cell.

AVIADO

Fuentes, J.: The Antagonistic Action of Sparteine upon the Veratrine Response. J. Pharmacol. & Exper. Therap. **119**: 225 (Feb.), 1957.

The similarities in circulatory effects between sparteine and quinidine include antiaccelerator activity (blockade of cardiac chronotropic action of epinephrine). Their effect on the skeletal muscle was investigated in terms of antagonizing the veratrine response (sustained contraction following electric stimulation of frog sartorius treated with veratridine). The antiveratrine activity of sparteine appears to be of the same order of potency as quinine and of veratramine (another veratrum alkaloid). The anti-accelerator activity of sparteine, on the other hand, is only 1/260 that of veratramine. The basic mechanisms of the 2 actions are probably unrelated.

AVIADO

Richardson, D. J., Lewis, W. H., Jr., Gahagan, L. H., and Sheehan, D.: Etiology and Treatment of Cardiac Arrhythmias Under Anesthesia for Electroconvulsive Therapy. New York J. Med. **57**: 881 (March 1), 1957.

The main signs and sources of cardiovascular strain in unmodified electroconvulsive therapy are cardiac arrhythmias (which may be vagal or extravagal in origin), paroxysmal hypertension, increased work of the heart, the Valsalva phenomenon, and hypoxia. The majority of the fatalities reported during or immediately after electroconvulsive therapy have been attributed to cardiovascular disturbances. The arrhythmias produced in treatment are the result of the electric stimulation of the brain, which sets into action a series of neurogenic or neuroendocrine responses. The vagal arrhythmias, which occur in about 30 per cent of nonatropinized patients, are characterized by marked slowing and occasional standstill of the heart and are preventable by adequate atropinization. In 40 per cent of the treatments with full atropinization there were rhythm disturbances necessarily classified as extravagal. Quinidine, chlorpromazine, and tetraethylammonium chloride have been used in attempting to prevent the extravagal arrhythmias. Tetraethylammonium chloride appears to be the most promising in this respect. It also alleviates the paroxysmal rise in arterial pressure induced by the electric stimulus.

HARRIS

Szabo, G., Solti, F., Rev, J., Refi, Z., and Megyesi, K.: Action of Chlorpromazine on Myocardial Hypoxia. Ztschr. Kreislaufforsch. **46**: 197 (March), 1957.

Fifteen normal persons were subjected to hypoxia through respiration of a 6 per cent oxygen mixture for 6 minutes, before and 10 minutes after intravenous injection of 25 mg. of chlorpromazine. After chlorpromazine the lowering of the T wave and the depression of the S-T segment that appeared previously no longer appeared in 8 persons and was less pronounced in 2. In 4 patients with angina pectoris 25 mg. 3 times daily for 5 to 7 days caused disappearance of the complaints in 2 and reduction of their intensity in 2; depression of the S-T segment after exercise was prevented in 2 and reduced in 1 patient.

LEPESCHKIN

Love, W. D., and Burch, G. E.: Differences in the Rate of Rb^{86} Uptake by Several Regions of the Myocardium of Control Dogs and Dogs Receiving l-Norepinephrine or Pitressin. J. Clin. Invest. **36**: 479 (March), 1957.

The left ventricle takes up Rb^{86} 45 per cent faster than the right ventricle or atria. Inner parts of the right ventricle took up Rb^{86} faster than the outer portion of the same ventricle. Pitressin and norepinephrine were observed to be associated with a more rapid uptake in the inner than in the outer portion of the left ventricle. Both pitressin and norepinephrine produced changes in uptake that resembled their previously established action on blood flow through the coronary arteries.

OPPENHEIMER

Love, W. D., and Burch, G. E.: A Study in Dogs of Methods Suitable for Estimating the Rate of Myocardial Uptake of Rb^{86} in Man, and the Effect of l-Norepinephrine and Pitressin on Rb^{86} Uptake. J. Clin. Invest. **36**: 468 (March), 1957.

The initial myocardial clearance of plasma Rb^{86} was observed to have a mean normal value of 70 ml. per 100 Gm. of ventricle. The standard error was 14 ml. per 100 Gm. of ventricle. Mean clearance over 30 minutes was 50 ml. with a standard error of 10 ml. The opinion was expressed that estimates of mean clearance were not suitable for detection of rapid uptake. However, the method does reliably reflect slow uptakes. This last statement is not true of turnover rates. Pitressin decreased and norepinephrine increased the initial plasma Rb^{86} clearance.

OPPENHEIMER

Melville, K. I., and Shister, H. E.: General Systemic Effects and Electrocardiographic Changes Following Injections of Digitalis Glycosides into the Lateral Ventricle of the Brain. Am. Heart J. **53**: 425 (March), 1957.

The direct injection of relatively small doses of digitalis glycosides (lanotoside C, Digoxin, and digitoxin) into the lateral ventricle through a previously placed cannula was found in unanes-

thetized cats to induce central nervous system excitation and cardiac arrhythmias. These efforts were accentuated rather than antagonized by potassium. It is postulated that these actions might be due to effects on central synaptic transmission involving acetylcholine. The authors also point out that these observations might explain some of the contradictory reports in the literature regarding the efficacy of potassium administration in the treatment of digitalis overdosage.

SAGALL

Rand, M., and Stafford, A.: The Influence of Ouabain on the Response of the Guinea-pig Heart to Acteylcholine, Adenosine and Vagal Stimulation. Arch. internat. pharmacodyn. **109**: 425 (Feb.), 1957.

The authors studied heart block produced in the guinea pig by adenosine, acetylcholine, and vagal stimulation, and the changes in this response brought about by ouabain. Guinea pigs were anesthetized with urethan (1.75 Gm. per Kg.). Acetylcholine chloride (100 μg. per ml.) and adenosine (1 mg. per ml.) were injected through a left atrial cannula. The right or left vagus was stimulated with square wave impulses. Vagal stimulation, acetylcholine and adenosine doses were adjusted to produce heart block lasting for about 4 seconds. Ouabain was dissolved in 0.9 per cent sodium chloride; a dose of 80 μg. per Kg. was used. Injection of ouabain potentiated the response to adenosine and acetylcholine, but did not affect the response to vagal stimulation. If doses of 65 to 190 μg. per Kg. were given the response to adenosine, acetylcholine, and vagal stimulation changed from heart block to ectopic impulse formation, originating in the ventricles. The action of acetylcholine was confined to a direct action on the myocardium. Potentiation of acetylcholine by ouabain occurred even in the presence of hexamethonium; it is, therefore, not due to sensitization of the ganglia.

SCHERF

Hilton, J. G., and Brown, R. V.: Blood Pressure Responses to Epinephrine under Various Anesthetic Agents. Arch. internat. pharmacodyn. **109**: 487 (Feb.), 1957.

The authors studied the effects of doses of epinephrine spanning the dosage from minimal to maximal blood pressure effects and compared the influence of various anesthetic agents upon these responses. The 4 anesthetic agents used were ether, chloralose, pentobarbital, and barbital. The dogs treated were maintained at as nearly the same depth of anesthesia as possible. Pentobarbital sodium was given in a dose of 30 mg. per Kg.; barbital sodium, 280 mg. per Kg.; cholralose, 110 mg. per Kg., and ether to maintain stage III, plane 3 anesthesia. Blood pressure was recorded from the right femoral artery with a mercury manometer and graded doses of l-epinephrine ranging from 0.1 to 10.0 mg. of l-epinephrine base per Kg. were injected.

At the highest doses studied, ether produced the greatest depression of the epinephrine response upon blood pressure. There were no significant differences between responses obtained under chloralose, barbital, and pentobarbital anesthesia, but there was a significant difference between the responses under pentobarbital and barbital anesthesia. At the intermediate dosage levels dogs under chloralose showed a greater response to epinephrine than that seen under any other anesthetic agent. The epinephrine dose responses were characteristic of the anesthetic employed.

SCHERF

PHYSICAL SIGNS

Stuckey, D., Dowd, B., and Walsh, H.: Cardiac Murmurs in School Children. M. J. Australia **1**: 36 (Jan. 12), 1957.

Of 34,863 school children aged 5 through 16 years in Sydney, routine health examination in 1955 disclosed a cardiac murmur in 467 (1.34 per cent). Three hundred and sixty-four of these were re-examined by 2 cardiologists; and, when organic heart disease was suspected, electrocardiographic and radiologic study was done. It was found that 36 had rheumatic heart disease, 72 had congenital heart disease, 239 had innocent systolic murmurs, and 17 had normal hearts with no murmur. The incidence of organic heart disease in this survey (4.2 per 1,000) was similar to that of comparable surveys in New York (5.0 per 1,000), in San Francisco (3.6-4.4 per 1,000) and in Toronto (3.6 per 1,000). However, the proportion of congenital heart disease was greater in the present survey (67 per cent) than in the other surveys (45 to 58 per cent) that were done years earlier.

ROGERS

Stuckey, D.: Innocent Systolic Murmurs of Aortic Origin. M. J. Australia **1**: 38 (Jan. 12), 1957.

Of 228 school children with heart murmurs investigated at the Royal Alexandra Hospital for Children, 145 were considered to have innocent systolic murmurs; and of these, 96 were regarded as being of aortic origin, although this point is speculative.

This murmur was brief and midsystolic in time. It was soft or moderate in intensity and was usually best heard at the mid or lower left sternal border, but occasionally it was loudest at the apex or in the aortic area. In nearly one half

of the patients it had a squeaky or musical character that distinguished it from the innocent pulmonic murmur. Organic mitral systolic murmurs differ by being pansystolic, by being heard in the axilla and, most importantly, by failing to be audible in the aortic area. The murmur of ventricular septal defect or of aortic stenosis is ordinarily louder, longer, accompanied by a thrill and is associated with other evidence of cardiovascular disease.

ROGERS

Snow, P. J. D.: The Sludging of Blood in the Retinal Veins. A Little-Known Physical Sign. Lancet **1**: 65 (Jan. 12), 1957.

In certain individuals pressure on the eyeball causes the column of blood in the retinal veins, as visualized with the ophthalmoscope, to become granular and then to form into larger discrete particles that move slowly toward the disk. The phenomenon occurred in certain diseases, in pregnancy, and (in mild form) in menstruation. Its usefulness appeared to be similar to that of the elevated sedimentation rate and the 2 phenomena were often but not invariably associated. Furthermore, it was sometimes associated with elevated serum globulin. The author proposes this test for the screening of patients with few or unconvincing symptoms.

MCKUSICK

PHYSIOLOGY

Schoop, W., and Pfleiderer, T.: Significance of a Local Regulatory Mechanism of Muscle Blood Flow during Intra-Arterial Infusion of Adenylic Acids. Ztschr. Kreislaufforsch. **46**: 304 (April), 1957.

In 10 normal persons and 13 patients with disturbances of the arterial circulation the blood flow through the calf, determined calorimetrically, showed in some cases a continuous increase for the duration of the infusion, while in others the increase was temporary. Still others showed oscillations of blood flow at a rate of about 1 in 2 minutes, which gradually decreased in amplitude; during these oscillations the flow reached values below the level before beginning the infusion. These differences can be best explained by a local counter-regulation of blood flow.

LEPESCHKIN

Knebel, R., and Wick, E.: Determination of Transmural Pressures in the Heart and Intrathoracic Vessels. Ztschr. Kreislaufforsch. **46**: 271 (April), 1957.

During registration of pressures with fluid transmission it is important to place the transducer at the exact level of the catheter opening. This can be determined algebraically from the linear displacement of the catheter shadow on the roentgen film caused by a given displacement of the tube. The normal intraesophageal pressure, measured in this way, oscillated from near 0 in expiration to —9 cm. of water in inspiration and the base line of the pulmonary artery pressure showed corresponding oscillations. The extramural pressure near the intracardiac catheter was determined by subtracting from the intraesophageal pressure the vertical distance between the esophageal and the cardiac catheters. The transmural pressure, determined by subtracting the extramural pressure from the absolute intracardiac pressure, was considerably higher than these absolute pressures, especially in patients with dyspnea.

LEPESCHKIN

Neuroth-Schmitt, G.: Distensibility and Contractility of the Isolated Frog Heart Under Different Conditions. Ztschr. Kreislaufforsch. **46**: 249 (April), 1957.

The curves representing the ventricular and atrial systolic and diastolic volumes of the isolated, perfused frog heart in relation to the filling pressure showed a higher course when the measurements were repeated. This corresponded to a decrease of diastolic tonus and systolic force of contraction. The trend was greater in rana esculenta than in rana temporaria. If the atrioventricular valves became insufficient or if the atrioventricular border was lightly ligated, the volume curves were displaced downward at medium filling pressures, while at low pressures the diastolic curve was displaced upward, the systolic curve downward. Repetition of the measurements under these conditions showed the same or even greater increase in contractility. These changes of myocardial tonus were not apparent in the quiescent ventricle, and were attributed to mechanical stimulation of nervous receptors in the atrium and ventricle.

LEPESCHKIN

Waud, R. A.: Blood and Hemodynamic Changes in Dogs Following Hemorrhagic Hypotension and its Treatment with Dextran. J. Pharmacol. & Exper. Therap. **119**: 85 (Jan.), 1957.

Dogs were hemorrhaged to a blood pressure of 50 mm. Hg and then transfused with an equal volume of dextran. Pyruvic and lactic acid values rose following bleeding but fell on transfusion. The injection of dextran also caused a fall in blood cholesterol, serum calcium, hemoglobin, and cell counts, which could all be due to the expected decrease in concentration when the blood volume was increased.

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ABSTRACTS DUE JUNE 13 FOR 1958 AHA SCIENTIFIC SESSIONS

The 1958 Scientific Sessions of the American Heart Association are scheduled to be held in the Civic Center, San Francisco, from Friday, October 24 through Sunday, October 26. Applications for the presentation of papers or for exhibit space may be obtained by writing to F. J. Lewy, M.D., Assistant Medical Director, American Heart Association. Applications will be processed by the Heart Association's Committee on Scientific Sessions Program.

Papers intended for presentation must be based on original investigation in, or related to, the cardiovascular field. Abstracts of such papers, *under no circumstances to exceed 300 words*, are due before Friday, June 13, 1958. They must be submitted in triplicate on forms which will be supplied to applicants. Space will be available in the Civic Center for scientific and technical exhibits.

RECORD ATTENDANCE SET AT SCIENTIFIC SESSIONS

A record-breaking attendance of 3,312, including 2,136 physicians and scientists and 81 medical students and nurses, was registered at the AHA Annual Meeting and Scientific Sessions in Chicago, October 25-29. The great variety of physicians attending included cardiovascular surgeons, internists, cardiologists and general practitioners, among others.

The special Scientific Sessions for Physicians in General Medicine, held for the first time this year, were attended by 490 physicians.

ARTERIOSCLEROSIS SOCIETY ANNUAL MEETING WITH AHA

The American Society for the Study of Arteriosclerosis will hold its 1958 Annual Meeting simultaneously with the 31st Annual Scientific Sessions of the American Heart Association in San Francisco, October 24-26. Several joint programs are being planned at that time.

The Society's new officers for the year are: R. Gordon Gould, Ph.D., Los Alamos, N. Mex., President; James C. Paterson, M.D., London, Ontario, Canada, Vice President; O. J. Pollak, M.D., Dover, Del., Secretary-Treasurer; and Forrest Kendall, Ph.D., New York, Program Chairman.

PHYSICIANS TO PLAY KEY ROLE IN 1958 HEART FUND DRIVE

Once again during the Heart Fund campaign throughout the month of February thousands of physicians will play key roles in the recruitment of community leadership and in acquainting the public with the facts concerning cardiovascular diseases and the Heart Association's research, community service and education programs.

The valuable role played by physicians in the campaign was pointed up by the Fund Raising Panel at the Association's Annual Meeting and Scientific Sessions in Chicago, October 25-29. Participating physicians said that the general public could best learn about local Heart rehabilitation and research programs through physicians speaking at meetings or taking part in press conferences and appearing on radio or television shows. They urged that more doctors assume leadership in the Heart Fund drive. John G. Smith, M.D., of Rocky Mount, N.C., is Chairman of the Association's Fund Raising Advisory and Policy Committee. Wendell B. Gordon, M.D., Pittsburgh, served as the Fund Raising Panel co-Chairman.

With a final national 1957 Heart Fund total

of $20,563,929, the 1958 objective has been set at $22,000,000. More than 50 per cent of the national office 1957 campaign income, or about $2,650,800, will be earmarked for research through grants-in-aid and the support of fellowships. Scientific research will also receive a substantial portion of the funds retained by local Heart Associations. Since 1948, when the Association became a national voluntary health agency, national, state and local Heart Associations have allocated more than $26,041,000 for research support.

Charles Perry McCormick of Baltimore, one of the nation's outstanding business and civic leaders, has been named 1958 Heart Fund National Campaign Chairman. Mrs. Dwight D. Eisenhower will serve as Honorary National Campaign Chairman, with Paul Dudley White, M.D. of Boston, as Honorary co-Chairman.

The most concentrated fund raising effort will take place on Heart Sunday, February 23, when an estimated million volunteers representing 56 affiliates and more than 350 chapters of the Heart Association will call on citizens throughout the nation for contributions.

HEART ASSOCIATION REAFFIRMS INDEPENDENT FUND POLICY

Reaffirmation of the policy of the American Heart Association to conduct independent fund campaigns rather than participate in United Funds was voted overwhelmingly by the national Assembly of the Association on October 29. Full concurrence in the action was given by the Association's Policy Committee meeting in New York, November 18.

An increasing number of Heart Associations were reported withdrawing from United Funds and community chests, with at least 93 Heart units which participated in federated drives in 1957 conducting independent campaigns in February. Since adoption of the Heart Association policy regarding united funds in 1955, a total of 171 Heart units have withdrawn from federated drives.

Robert W. Wilkins, M.D., of Boston, President of the American Heart Association, said that "our experience over the years with United Funds has proved conclusively that the independent Heart Fund campaign is the best way to finance the Heart Association's expanding program of research, education and community service. Any infringement on the public's right to contribute to the Heart Fund directly and freely, in amounts it chooses, can delay the conquest of heart disease and cause untold suffering and loss of life."

AMA PRESIDENT-ELECT WARNS OF "COMPULSORY METHODS"

Gunnar Gundersen, M.D., President-Elect of the American Medical Association, in an address at the 30th Annual Scientific Sessions of the Heart Association in Chicago, October 26, warned of a drift toward "compulsory methods" and "government programs" and called for closer cooperation between Heart Association affiliates and state and county medical societies. One of the major aims of AMA for the future, Dr. Gundersen said, "is to achieve a closer liaison and better relationship with voluntary health organizations."

CARDIOLOGY CONGRESS ABSTRACTS DEADLINE IS FEBRUARY FIRST

Abstracts of papers to be presented at the Third World Congress of Cardiology, September 14-21, in Brussels, must be sent to Dr. F. J. Lewy at the American Heart Association's national office to arrive prior to February 1, 1958. Abstracts should consist of not more than 200 words in English, typed in double-space, with a translation in either French, Spanish or German. All other information on the forthcoming Congress may be obtained from Dr. F. Van Dooren, Secretary of the Congress, 80 Rue Mercelis, Brussels, Belgium.

The Belgian Society of Cardiology has announced receipt of a gift of 100,000 Belgian francs from the Professional Union of Insurance Organizations to serve as a prize for the best original cardiology paper submitted by a doctor under 50 years of age.

It was also announced by Paul Dudley White, M.D., that he has arranged for his secretary, Miss Helen Donovan, to attend the Congress and assist participating American physicians. Miss Donovan served during the Second World Congress of Cardiology.

GRANT PERMITS YOUNG RESEARCHERS TO ATTEND CARDIOLOGY CONGRESS

The American Heart Association has received a special grant from the National Heart Institute to permit a limited number of research scientists in the cardiovascular field to attend the Third World Congress of Cardiology in Brussels, Belgium, September 14-21. The funds will provide for round trip air travel from New York City to Brussels plus a per diem allotment during the Congress. Younger investigators who would otherwise be likely to experience difficulty in obtaining funds for this purpose will be given preference. Requests for information and application blanks should be addressed to the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N.Y. Deadline for applications is February 20, 1958.

PIONEERS IN FIELD TO LEAD ANTICOAGULANTS SYMPOSIUM

A symposium on the "Historical and Physiological Aspects of Anticoagulants," which will feature the actual pioneers in the development of this treatment, will be held on February 25, at the New York Academy of Medicine, 103rd Street and Fifth Avenue, New York City. The unique meeting is under the auspices of the New York Heart Association and the Section of Medicine of the New York Academy of Medicine.

Participants include Irving S. Wright, M.D. Professor of Clinical Medicine, Cornell University Medical College; Jay McLean, M.D., Director, Radiation Therapy, Savannah Tumor Center, Savannah, Ga.; Charles Best, M.D., Professor of Physiology, University of Toronto; Armand J. Quick, M.D. Professor of Biochemistry, Marquette University Medical College, Milwaukee; and Karl Paul Link, Professor of Chemistry, University of Wisconsin.

BLOOD PRESSURE COUNCIL ELECTS NEW OFFICERS

The Council for High Blood Pressure Research of the American Heart Association which met in Cleveland, November 22-23, chose Eric Ogden, M.D., of Columbus, as Chairman and Keith S. Grimson, M.D. of Cleveland, as Vice Chairman of its Medical Advisory Committee. Other Council officers, all from Cleveland, are: Maynard H. Murch, President; Frank E. Joseph, Vice President; George E. Merrifield, Secretary; and I. F. Freiberger, Treasurer. Proceedings of this meeting will be available in the near future.

"STROKES" FILM AVAILABLE

President Eisenhower's latest illness has stimulated interest in the American Heart Association's new film, "Strokes," which is available from the national office or through local Heart Associations. The color film, approximately six minutes long, provides an excellent visual aid to physicians addressing lay groups and is particularly suited for television use.

SUBSCRIPTION RENEWALS

Renewal of subscriptions for *Circulation* and *Circulation Research*, official journals of the American Heart Association, should be made directly through the publisher, Grune and Stratton, Inc., 381 Fourth Avenue, New York, 16, N.Y. Both members and non-members of the Heart Association may renew their subscriptions in this manner.

NATIONAL HEALTH FORUM SCHEDULED IN MARCH

The 1958 National Health Forum, to be held March 18-20 at the Sheraton Hotel, Philadelphia, will be concerned with the health problems growing out of the "urban sprawl which is developing all across the country."

The Forum, sponsored each year by the National Health Council in behalf of its 59 national organization members, will be under the co-chairmanship of Abel Wolman, M.D., Professor of Sanitary Engineering at Johns Hopkins University, and Frank C. Moore, President of the Government Affairs Foundation.

MEETINGS CALENDAR

February 12-14: American Academy of Occupational Medicine, New York. Leonard J. Goldwater, M.D., 600 West 168th Street, New York, N.Y.

March 9-14: International College of Surgeons, 11th Biennial Congress, Los Angeles. Karl A. Meyer, M.D., 1516 Lake Shore Drive, Chicago 10, Ill.

March 10-13: Southeastern Surgical Congress, Baltimore. B. T. Beasley, M.D., 45 Edgewood Avenue, S.E., Atlanta 3, Ga.

March 20-22: Chicago Heart Association, Conference on Pulmonary Circulation, Chicago. Wright Adams, M.D., Department of Medicine, University of Chicago.

March 24-27: American Academy of General Practice, 10th Annual Scientific Assembly, Dallas. Mac F. Cahal, Volker B'lvd. at Brookside, Kansas City 12, Mo.

March 29-30: American Psychosomatic Society, Cincinnati. Morton F. Reiser, 55 Madison Avenue, New York 22, N.Y.

April 16-18: American Surgical Association, New York. R. K. Gilerist, 59 E. Madison Street, Chicago 3, Ill.

April 24-26: Fifth International Congress of Internal Medicine, Philadelphia. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 28-May 2: American College of Physicians, Atlantic City. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 1-4: Student American Medical Association, Chicago. Russell F. Staudacher, 510 N. Dearborn, Chicago 10, Ill.

May 4: American Federation for Clinical Research, Atlantic City. William W. Stead, VA Hospital, Minneapolis 17, Minn.

May 5: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N.Y.

May 6-7: Association of American Physicians, Atlantic City. P. R. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 8-9: American Pediatric Society, Atlantic City. A. C. McGuinness, 2800 Quebec Street, N.W., Washington 8, D.C.

June 19-22: American Medical Womens Association, San Francisco. Miss L. T. Majally, 1790 Broadway, New York 19, N.Y.

June 23-27: American Medical Association, San Francisco. George F. Lull, 535 N. Dearborn, Chicago 10, Ill.

ABROAD

January 21-February 14: International Union of Biochemistry, General Assembly, Vienna, Austria. Prof. R. H. J. Thompson, Department of Chemical Pathology, Guy's Hospital Medical School, London, S.E. 1, England.

April 16-19: International Academy of Legal Medicine and Social Medicine, 50th International Congress, Madrid. Prof. B. Piga, Professor of Legal Medicine, Madrid University, Madrid, Spain.

July 15-21: Medical Women's International Association, London. J. Aitken, M.D., 30A Acacia Road, London, N.W. 8, England.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

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CONTENTS